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RELATION OF SERUM CALCIUM TO PATHOLOGIC CALCIFICATIONS OF HYPERVITAMINOSIS D

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The mechanism by which the calcifications of hypervitaminosis D are produced is largely of interest because of the information which may be gained from its study regarding many rather complex features of the calcium metabolism. Once the calcifications are regarded as the result of the precipitation of calcium salts from the serum rather than as the aftermath of the toxic effect of the vitamin on the tissues, the scope of this field of research is enormously increased. The present contribution is concerned with a study and interpretation of the evidence obtained by correlating the changes in the tissues with the serum calcium curves of animals during the time immediately following the administration of one single massive dose of activated ergosterol.

MATERIAL AND METHODS

Forty-eight rats and five rabbits were used in the experiments, and these were divided into four series.

Series 1 consisted of seven rats. Two were used as controls, and five were each given 0.4 cc. of activated ergosterol [1] 10,000 × at the beginning of the experiment.

Series 2 consisted of five rabbits, each of which received 2.5 cc. of activated ergosterol 10,000 × at the beginning of the experiment. They were killed at different intervals up to ninety-six hours. Determinations of blood calcium were made, not only immediately before death but also throughout the course of the experiment.

Series 3 consisted of thirty-one full grown male rats, four of which were used as controls. The remainder each received 0.5 cc. of activated ergosterol 10,000 × at the beginning of the experiment. These animals were killed at close intervals, the last group being killed one hundred and twelve hours after the beginning of the experiment.

Series 4 consisted of ten young male rats of an average weight of approximately 150 Gm. Two were utilized as controls, and the remainder each received 0.75 cc. of activated ergosterol 10,000 × at the beginning of the experiment. They were killed at intervals up to seventy-two hours.

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1. Footnote deleted.

In all series the animals were fed on stock laboratory diets. In addition to their regular diet the rabbits each received 15 grains (0.97 Gm.) of calcium lactate per day, which was administered in their drinking water. The activated ergosterol was administered to the rats with their food, and to the rabbits by introducing it into their mouths with a dropper. The animals were killed in all cases by ether anesthesia. Blood for calcium determinations was taken from the rabbits by cutting small vessels in the ear and allowing the blood to flow into a tube. It was obtained from the rats, while they were under anesthesia, by cutting the tail and allowing the blood to escape into a tube. If 5 cc. could not be obtained by this procedure, recourse was taken to a cardiac puncture. At autopsy, blocks were taken from the heart, aorta, lung, liver, spleen, kidney, parathyroid and thyroid. The incisor teeth were also removed for study and will be reported on separately. Because of the inaccuracy of the usual methods of staining for calcium, (Cameron [2]) the tissues in series 1 and 2 were fixed in alcohol and a solution of formaldehyde in order to prepare sections for incineration (Policard [3]). Estimates of serum calcium were made by the Collip and Clark modification of the Tisdall-Kramer method. The serum was prepared by incubating the blood for

OBSERVATIONS

TABLE 1.—*Observations in Series 1*

Rat	Hours After Receiving Ergosterol	Serum Calcium Before Death, Mg. per 100 Cc.	Calcification of Coronary Vessels	Calcification of Aorta
1	0	8.9	Negative	Negative
2	0	8.6	Negative	Negative
3	18	12.2	Negative	Negative
4	24	14.4	Negative	Negative
5	30	15.9	Negative	Negative
6	48	17.6	Slight	Slight
7	72	16.1	Positive	Positive

half an hour at 37 C., after which the clot was loosened by an applicator and the tube placed in an icebox for two hours. After centrifugation at high speed the serum was pipetted off and the calcium estimation made.

SERIES 1.—*Microscopic Examination.*—Sections from both the rats used as controls and the test rats killed early in the experiment showed considerable variation in the color and intensity of the hematoxylin staining. Furthermore, there was present in both the control and the experimental rats some degree of vacuolation in the cellular areas between the elastic plates of the aorta. In the stained sections no definite lesions were found in the aorta until the sections from rat 7 were examined, and they showed the lesion typical of hypervitaminosis D in that location. In the early specimens the sections of cardiac muscle showed some variability in staining qualities, and in rat 6 a slight infiltration by inflammatory cells was noted about one of the branches of a coronary vessel. No areas of calcification as depicted with hematoxylin were noted in the sections from rat 6. Rat 7 showed areas of marked deposition of calcium in the sections from both the aorta and the heart. There were also many areas of infiltration of the cardiac muscle by inflammatory cells. These were usually situated about the smaller branches of the coronary vessels. The series of sections which were

2. Cameron, J. R.: J. Path. & Bact. **33**:929, 1930.
3. Policard, A.: Protoplasma **7**:464, 1929.

incinerated showed no increase of mineral content in the aorta or heart until the sections from rat 6 were examined; these showed a slight but definite increase in mineral in the inner third of the media in some areas. Sections from the heart of rat 6 showed the walls of small branches of the coronary vessels to contain more mineral than was usual in the preceding sections. The sections from rat 7 showed marked amounts of mineral matter in both the aorta and the heart in the locations described.

Correlation of Pathologic Changes With Estimations of Serum Calcium.—After the administration of the activated ergosterol the serum calcium level ascended for approximately forty-eight hours and then began to fall. Calcifications first appeared when the peak of the curve had been reached, but were not prominent until the curve had begun to fall. Thus the appearance of marked calcifications in the tissues was associated with the beginning of the fall of the serum calcium curve.

SERIES 2.—*Microscopic Examination.*—All the rabbits, with the exception of rabbit 5, showed calcifications of recent origin in the inner third of the aortic media. In the stained sections swollen areas situated between adjacent elastic plates were evident in the inner third of the media. In these areas a considerable

TABLE 2.—*Serum Calcium Levels in Series 2*

	Mg. of Calcium per Hundred Cubic Centimeters of Serum at Given Number of Hours After Rabbit Received Ergosterol				
Rabbit	0	24 Hours	48 Hours	72 Hours	96 Hours
5	16.4	15.5*			
6	14.0	13.8	17.1	14.5*	
7	15.0	14.4	15.4	18.8	14.3*
8	13.4	13.3	13.3*		
9	14.0	16.1	13.3	11.5*	

* Postmortem examination made.

amount of material staining a deep blue was encountered, some of which was associated with elastic fibers; other portions of it were related to the cells of the areas between adjacent elastic plates, and some of it was amorphous. The edematous nature of the area in which the deposition of calcium occurred was striking, and was apparently of sufficient importance to cause a compression of the cellular areas between the adjacent elastic plates. The incinerated sections of the aorta showed the described areas to contain greatly increased amounts of mineral matter. The sections of cardiac muscle showed some calcification of muscle, but the small branches of the coronary vessels did not show the extensive lesions seen in the hearts of the rats.

Correlation of Pathologic Changes With Estimations of Serum Calcium.—The response of the serum calcium to the administration of activated ergosterol was exceedingly variable in the rabbits. In two, rabbits 5 and 8, there was little change of significance, yet recent calcification was very obvious in the aorta of rabbit 8. In rabbit 6, there was little change for the first twenty-four hours, but a marked upswing occurred in the second twenty-four hours and a marked downswing during the third twenty-four hours. In rabbit 7 the great part of the upswing occurred in the period between forty-eight and seventy-two hours after the administration of the ergosterol, and then a marked drop occurred between this time and ninety-six hours. In rabbit 9, a rather mild upswing occurred in the first twenty-four hours, and this was followed by a drop which lasted for the next

forty-eight hours and carried the serum calcium far below its original level. As all the animals, with the exception of rabbit 5, showed recent calcifications in the aortic wall, it is obvious that calcium was deposited in the tissues when the serum calcium level had shown either little change or a marked rise followed by a fall.

TABLE 3.—*Observations in Series 3*

Rat	Hours After Receiving Ergosterol	Serum Calcium Before Death, Mg. per 100 Cc.	Calcification in Heart and Coronary Vessels	Calcification in Aorta
1	0	0.8	Negative	Negative
2	0	9.8	Negative	Negative
3	0	10.6	Negative	Negative
4	0	10.9	Negative	Negative
5	16	11.2	Negative	Negative
6	16	11.0	Negative	Negative
7	16	12.9	Negative	Negative
8	24	12.1	Negative	Negative
9	24	12.1	Negative	Negative
10	24	13.0	Negative	Negative
11	40	13.0	Negative	Negative
12	40	13.0	Negative	Negative
13	40	13.6	Negative	Negative
14	48	13.0	Negative	Negative
15	48	15.5	Negative	Negative
16	48	15.9	Negative	Negative
17	64	14.9	Negative	Negative
18	64	15.1	Negative	Negative
19	64	14.7	Positive	Negative
20	72	16.3	Negative	Negative
21	72	17.0	Negative	Negative
22	72	12.2	Negative	Negative
23	88	14.5	Negative	Positive
24	92	16.1	Negative	Negative
25	92	12.6	Negative	Negative
26	92	12.4	Negative	Positive
27	113	13.7	Negative	Negative
28	113	13.9	Negative	Negative
29	113	13.4	Negative	Positive
30	113	Not done	Negative	Positive
31	113	14.4	Negative	Positive

TABLE 4.—*Observations in Series 4*

Rat	Hours After Receiving Ergosterol	Serum Calcium Before Death, Mg. per 100 Cc.	Calcification of Coronary Vessels	Calcification in Aorta	Inflammatory Cell Infiltration
1	0	10.3	Negative	Negative	Negative
2	0	10.3	Negative	Negative	Negative
3	24	10.0	Negative	Negative	Negative
4	24	13.0	Negative	Negative	Negative
5	48	17.4	Negative	Negative	Negative
6	48	16.3	Slight	Negative	Slight
7	72	17.0	Marked	Marked	Marked
8	72	14.7	Positive	Marked	Marked
9	72	15.3	Positive	Marked	Marked
10	72	Not done	Marked	Marked	Positive

SERIES 3.—*Microscopic Examination.*—The hearts and aortas of this series of rats were examined by means of both stained and incinerated sections. Only a few of the rat aortas revealed areas of calcification. Sections of the heart showed only rarely a calcified coronary vessel. There were mild infiltrations by inflammatory cells about the smaller coronary vessels in the cardiac musculature of several of the animals in the latter part of the series.

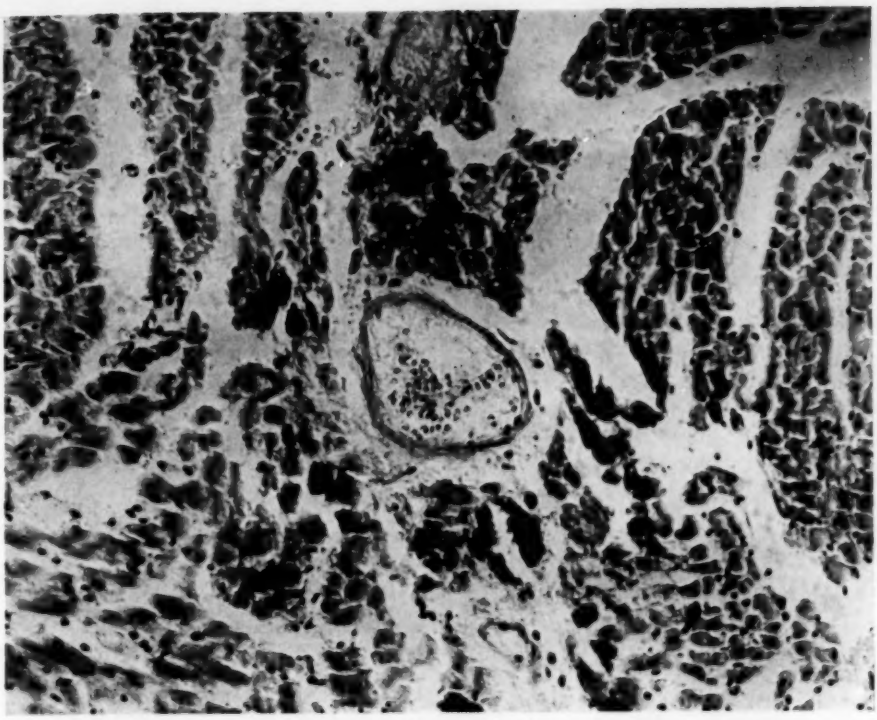

Fig. 1.—Photomicrograph of section of cardiac muscle from rat 10, series 4; hematoxylin and eosin stain; × 200. The picture demonstrates marked calcification of the muscle with little evidence of infiltration by inflammatory cells.

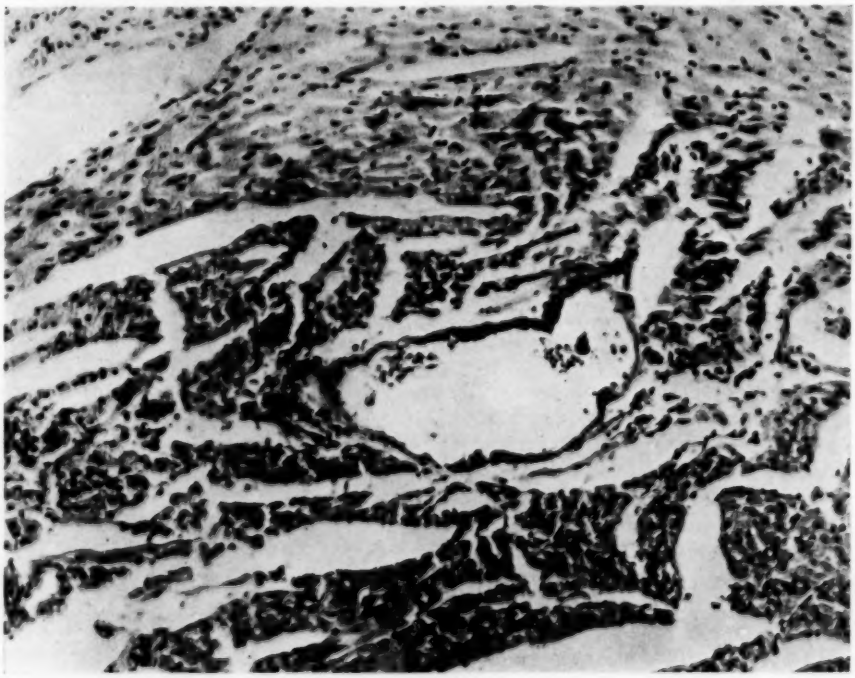

Fig. 2.—Photomicrograph of section of cardiac muscle from rat 7, series 4; hematoxylin and eosin stain; × 120. The picture shows a lesion demonstrating both marked calcification and infiltration by inflammatory cells. Calcification of the wall of the blood vessel is pronounced.

Correlation of Pathologic Changes With Estimations of Serum Calcium.—In this series of rats the highest calcium readings were found in those killed at the end of seventy-two hours. Up to that time the animals demonstrated a gradual rise in the calcium content of the serum and after that time a more or less irregular fall. The first animal to demonstrate calcifications showed a serum calcium level near the peak of the curve; in all the others the curve was on the downswing. It is significant that only some of these animals demonstrated lesions, and the lesions were not nearly so well marked as those of the next series to be described.

SERIES 4.—*Microscopic Examination.*—Although the sections from rat 6 showed evidences of slight deposition of calcium in the aorta and heart, marked lesions were not found until the sections from the last four rats were examined.

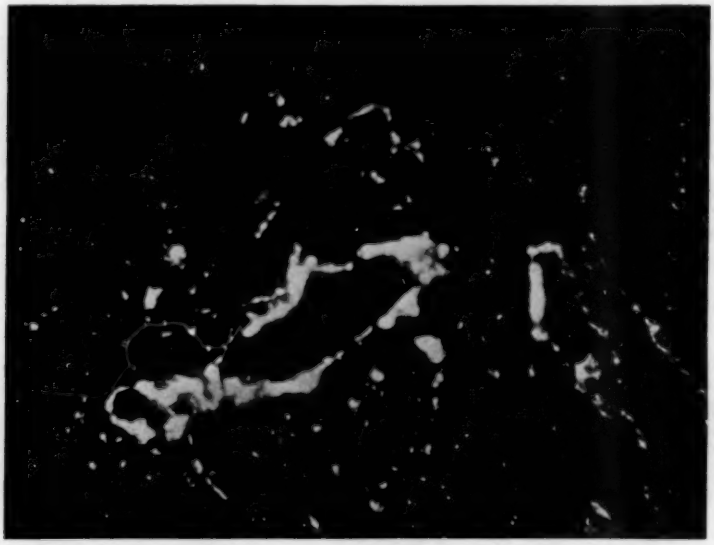

Fig. 3.—Dark-field photomicrograph of a calcified coronary vessel from rat 7, series 4; incinerated specimen; × 180. The increased amount of mineral matter in the wall of the blood vessel may be seen against the black background.

Sections from the aortas revealed the lesions to be situated in the inner third of the media, and to present the same appearance as those already described in this paper and in a previous contribution (Ham [4]). The lesions in the cardiac musculature showed a certain variability in appearance. One type of lesion demonstrated marked calcification with little infiltration by inflammatory cells (rat 10, fig. 1). Another type illustrated a marked infiltration by inflammatory cells with only a moderate amount of calcium deposition (rats 8 and 9). A third type of lesion showed a marked amount of calcium deposition with a marked infiltration by inflammatory cells (rat 7, fig. 2).

Correlation of Pathologic Changes With Estimations of Serum Calcium.—In this series of animals the peak of the serum calcium curve appeared to be reached

4. Ham, A. W.: Arch. Path. **14**:613, 1932.

in between forty-eight and seventy-two hours. In one instance slight calcification appeared at the end of forty-eight hours, but immediately after this time the calcifications became marked. Although some calcification was found at the time of the greatest hypercalcemia, deposits of calcium were found in much greater amounts after enough time had elapsed for the calcium of the serum to begin its fall.

It is significant that in general the activated ergosterol demonstrated a very constant effect in the three series of rats. Shortly after its administration the serum calcium began to rise, and a peak was reached in somewhere between twenty-four and seventy-two hours. It is unfortunate that estimations of calcium could not be made frequently from the same animals, but it is difficult to obtain even once sufficient blood for a calcium determination, particularly if young rats are used, and from these experiments and others which have been reported (Ham [4]) young rats appear to be affected to a greater extent than older ones. Rabbits are known to possess a very unstable calcium metabolism, and the results in this paper bear out this conclusion. Although in most instances a change in the level of the serum calcium occurred, in one instance calcifications were produced with little change in the serum calcium level; the significance of this observation will be discussed later in detail. It is also obvious that series 4 was the best, so far as this study is concerned, because sufficient ergosterol was given to cause marked, definite lesions in every instance in which the animal was allowed to live a sufficient length of time. In this work calcifications are regarded as stainable with hematoxylin, although we are well aware of the possibilities of error in this connection, but it is felt, because of previous work (Ham [4]), that this staining method is sufficiently reliable in this type of experiment, particularly when controlled with incineration.

COMMENT

Pathologic calcifications have been divided into two general types, those which are dependent on degenerative changes in the recipient tissues and those which are dependent on the inability of the serum and tissue fluid to retain all its calcium in solution (Ham [5a]). Recognized examples of the latter type in man have been described by several authors, and it is known that in many instances they are associated with parathyroid tumors and in other instances with disease of the bone not associated with or caused by parathyroid tumors. The literature in this field has recently been reviewed completely by Barr.[6] It is well known, moreover, that calcifications of this type have been pro-

5. Ham, A. W.: (*a*) Cartilage and Bone, in Cowdry: Special Cytology, ed. 2, New York, Paul B. Hoeber, Inc., 1932; (*b*) Angle Orthodontist **2**:142, 1932.

6. Barr, D. P.: Physiol. Rev. **12**:593, 1932.

duced experimentally by intraperitoneal and intravenous injections of calcium salts (Tanaka,[7] Katase [8]), by the intraperitoneal injection of calcium gluconate (McJunkin, Tweedy and Breuhaus,[9]), by the injection of large amounts of parathyroid hormone (Hueper,[10] McJunkin, Tweedy and Breuhaus [9] and others), by the administration of massive doses of vitamin D (by a host of investigators) and by varying the reaction of a diet high in calcium in mice (by Rabl [11] and by Butler [12]).

It is therefore evident that calcium salts may be precipitated from the serum and tissue fluid into the tissues themselves. At first thought it may seem that this phenomenon is nothing more than the result of a hypercalcemia, but investigation has demonstrated this explanation to be inadequate. Shelling [13] found that calcification of this variety occurred in parathyroidectomized animals when they were given sufficient phosphate in their diet. He also showed [14] that the parathyroidectomized animals were more susceptible to the action of vitamin D in producing calcifications than were normal animals. In both these instances it is apparent that calcifications were produced without the advent of hypercalcemia. Smith and Elvove [15] in their experiments with ergosterol poisoning found that on some occasions enormous deposits of calcium were associated with little change in the serum calcium level, whereas on other occasions marked increases of the serum calcium level were not associated with precipitations in the tissues. Furthermore, one rabbit in series 2 showed extensive calcifications with little change in the serum calcium level, whereas many of the rats in series 3 that showed considerable change in the serum calcium level showed little in the way of calcium deposits. It seems apparent that the hypercalcemia in itself is not sufficient to account for the calcifications—a conclusion already postulated by Smith and Elvove.

As the level of the serum calcium does not bear a definite or constant relationship to the precipitation of calcium salts into the tissues, it becomes evident that the state of the serum calcium must be investigated for the answer to the problem. The blood is known to contain more calcium than can be explained by the laws of simple solution. The factors in this phenomenon have recently been comprehensively

7. Tanaka, M.: Biochem. Ztschr. **35**:113, 1911.
8. Katase: Beitr. z. path. Anat. u. z. allg. Path. **57**:516, 1914.
9. McJunkin, F. A.; Tweedy, W. R., and Breuhaus, H. C.: Arch. Path. **14**:649, 1932.
10. Hueper, W.: Arch. Path. **3**:14, 1927.
11. Rabl: Virchows Arch. f. path. Anat. **245**:542, 1923.
12. Butler, M.: Proc. New York Path. Soc. **24**:79, 1924.
13. Shelling, D. H.: Proc. Soc. Exper. Biol. & Med. **28**:301, 1930.
14. Shelling, D. H.: Proc. Soc. Exper. Biol. & Med. **28**:303, 1930.
15. Smith, M. I., and Elvove, E.: Pub. Health Rep. **44**:1245, 1929.

reviewed by Peters and Van Slyke.[16] There is evidence to show the existence of at least three fractions in the serum calcium: first, a relatively small portion which is held in solution by the forces which ordinarily govern solubility in salt solutions; second, a portion which is held in solution by the serum proteins, and third, a portion which is held in solution by unknown factors which appear to be greatly influenced by the presence of the parathyroid hormone. A certain amount of evidence indicates the portion of the serum calcium associated with the parathyroid hormone to be nondiffusible (Cameron and Moorhouse,[17] Cameron [18]), although there is controversy on this point (Morgulis and Perley [19]). Furthermore, there appears to be a kind of equilibrium between the various fractions of the serum calcium and the calcium of the bones. The literature regarding this phase of the problem has been reviewed in previous contributions (Ham [5]).

There is now a considerable amount of evidence to indicate that vitamin D acts on the serum calcium level in a manner identical with that of the parathyroid hormone. The absence of either parathyroid hormone or vitamin D in growing animals results in rachitic changes in the growing zones of the long bones. The long-continued administration of either parathyroid hormone (Jaffe and Bodansky [20]) or vitamin D (Grauer [21]) in huge doses results in a marked loss of mineral salts from the skeleton, and the bones in both instances demonstrate the changes characteristic of osteitis fibrosa cystica. Furthermore, large doses of either substance may result in the production of metastatic calcification. Although the action of vitamin D in parathyroidectomized animals is frequently discussed in the literature, it is probable that complete parathyroidectomies are extremely difficult to accomplish because of the widespread distribution of these glands. It is significant that the experiments of Taylor, Branion and Kay [22] demonstrated the inability of large doses of vitamin D to raise the serum calcium levels of dogs sufficiently to prevent tetany after extraordinarily complete dissection of the neck, although the same dosages of vitamin D prevented tetany when the usual parathyroidectomy had been performed. There is therefore good reason to believe that vitamin D accomplishes its action on the serum level through the agency of the parathyroid gland,

16. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1931.

17. Cameron, A. T., and Moorhouse, V. H. K.: J. Biol. Chem. **63**:687, 1925.

18. Cameron, A. T.: Canad. M. A. J. **16**:759, 1926.

19. Morgulis, S., and Perley, A. M.: J. Biol. Chem. **88**:169, 1930.

20. Jaffe, H. L., and Bodansky, A.: J. Exper. Med. **52**:669, 1930.

21. Grauer, R. C.: Proc. Soc. Exper. Biol. & Med. **29**:466, 1932.

22. Taylor, N. B.; Branion, H. D., and Kay, H. D.: J. Physiol. **69**: Proc. xxxv, 1930.

although it is also conceivable that it may act through the activation of the hormone rather than on the gland.

Consequently there is evidence to show that the calcifications associated with hypervitaminosis D depend on a precipitation of calcium from the serum, and furthermore that this precipitation is more dependent on the state of the serum calcium than on its level. As it is most probable that vitamin D exerts its effect on the calcium metabolism through the parathyroid mechanism, the calcifications associated with hypervitaminosis D can be explained as being dependent on the shifting about of calcium between the various fractions of the serum, the tissues and the intestine when the vitamin is administered in enormous amounts. As the appearance of the pathologic calcifications is associated with the downswing of the serum calcium curve following a single massive dose of the vitamin, it seems probable that the distribution of calcium in the various fractions in the serum is considerably changed throughout the course of a rise and fall in the serum curve induced by vitamin D. During the upswing, the shift in calcium toward the serum could be accounted for by the attraction of the increased amount of parathyroid hormone in the circulation or by its increased ability to attract calcium. The shift could be represented diagrammatically as follows:

Fraction of serum calcium controlled by parathyroid hormone	←	Fraction of serum calcium in simple solution

Fraction of serum calcium in simple solution ← Bones
Fraction of serum calcium in simple solution ← Other tissues
Fraction of serum calcium in simple solution ← Intestine

Thus the amount of the serum calcium is increased at the expense of the bones, other tissues and calcium in the intestine.

After the height of the hypercalcemia is attained, the serum calcium begins to fall because the parathyroid hormone in the blood no longer exerts the same attraction for calcium. The release of calcium from this fraction of the serum calcium therefore induces a shift of the equilibrium in the other direction. This shift may be represented diagrammatically as follows:

Fraction of serum calcium controlled by parathyroid hormone	→	Fraction of serum calcium in simple solution

Fraction of serum calcium in simple solution → Bones
Fraction of serum calcium in simple solution → Other tissues
Fraction of serum calcium in simple solution → Intestine
Fraction of serum calcium in simple solution → Urine

As the serum retains only a small amount of the total serum calcium in simple solution, it is evident that if the release of calcium from the greatly increased fraction associated with the parathyroid hormone is at all rapid, precipitations of calcium salts will be forced, and although much of the liberated calcium is deposited in the bones or excreted by

way of the kidney or intestine, there is a distinct possibility of calcium salts being precipitated in the tissues.

Thus it is thought that the observations in this series of experiments indicate that the mechanism of calcification in hypervitaminosis D depends primarily on the release of calcium from the parathyroid hormone-controlled fraction of the serum calcium, so that the serum is unable to retain in simple solution the calcium thus liberated. Other factors, such as the phosphate content of the serum, the carbon dioxide tension and the physicochemical affinity of certain tissues for calcium salts, are concerned in the mechanism of calcification, but their action is dependent on the degree of saturation of the serum with calcium in simple solution. It also appears that the utilization of a single dose of vitamin D allows an excellent opportunity to study the problem, as it seems logical to consider the shift in calcium as occurring toward the blood and particularly toward the parathyroid hormone-controlled fraction on the upswing of the serum calcium curve, and in the reverse direction as the serum calcium level falls.

Barr [6] and Peters and Van Slyke [16] in their recent reviews considered the portion of the serum calcium associated with the parathyroid hormone to be physiologically active because of the therapeutic action of the hormone in tetany and its toxic action in excessive dosages. It is questionable, however, whether this conclusion needs to follow from their evidence. If the fraction of the serum calcium governed by the parathyroid hormone is in a kind of equilibrium with the fraction which is held in solution by the forces ordinarily governing solubility in salt solutions, and this fraction in turn is also in equilibrium with the calcium reservoirs (the bones and possibly other tissues), it is seen that the administration of parathyroid hormone can result in nothing more than a shift in calcium from the bones, tissues and intestine toward the parathyroid hormone-controlled fraction of the serum calcium, which will in this case be greatly increased. Thus one does not expect to see pathologic calcifications appearing as the shift occurs in this direction (while the serum calcium is rising, following a single dose). On the other hand, as soon as the serum calcium begins to fall, because of the gradually diminishing calcium-binding effect of the administered parathyroid hormone, one expects the portion of the serum calcium in simple solution to reach rapidly a saturated state, so that the further liberation of calcium from the parathyroid-controlled fraction will result in the deposition of calcium salts in the bones, and if the process is sufficiently rapid, in the tissues as well. In the experiments reported in this paper it is obvious that the deposition of calcium in the tissues occurred in the rats when the serum calcium curve had attained its peak and was beginning to fall, a time that would correspond with the release of calcium from the parathyroid-controlled fraction. Thus the so-called

toxic effect of parathyroid hormone can be explained without assuming the fraction of the serum calcium controlled by it to be physiologically active.

The evidence regarding the ability of the parathyroid hormone to relieve tetany is likewise not proof that the portion of the serum calcium associated with it is physiologically active. Its use in this condition is to increase the fraction of the serum calcium that it controls at the expense of the other calcium of the serum as well as that of the tissues, bones and intestine. Although its first effect may be a temporary lowering of the part of the serum calcium which is in true solution and physiologically active because of its ionization, it is obvious that equilibrium quickly becomes established at a higher level so that the amount of the serum calcium in simple solution shortly becomes increased. It is significant that it is not uncommon for the first dose of vitamin D in severe cases of clinical rickets to precipitate an attack of tetany, from which the patient soon recovers. Furthermore, the experimental procedure of temporarily increasing the depth of tetany by the administration of vitamin D has been reported on by Taylor,[23] although his explanation differs from the one just given.

It is therefore possible to explain the therapeutic and toxic effects of vitamin D and parathyroid hormone without assuming the portion of the serum calcium associated with the parathyroid hormone to be physiologically active. If one keeps in mind the possibility of the shift of calcium between the intestine, bones and tissues and the various fractions of the serum, it is possible to explain many of the complex and apparently paradoxical features of the calcium metabolism. The reason for the ability of the serum, under the influence of parathyroid hormone or vitamin D, to take up more calcium than it is subsequently able to hold in solution becomes apparent, as does the ability of these substances to cause a depletion of the bones followed by precipitation in the soft tissues. Likewise the ability of vitamin D readily to cause calcifications in partially parathyroidectomized animals is explained if one remembers that the shift of calcium from the parathyroid-controlled fraction to the tissues is relatively extensive because of the almost complete dissolution of the parathyroid-controlled fraction after the temporary vitamin D stimulus has disappeared. Furthermore the ease with which pathologic calcifications may be produced in partially parathyroidectomized animals is understood if one appreciates the equilibrium-maintaining function of the parathyroid hormone in the serum. In its partial or complete absence the addition of other ions to the solution (as the introduction of phosphate) may force out precipitations of calcium, while in its presence the excess calcium ions can be taken up by the

23. Taylor, N. B., and Weld, C. B.: Tr. Roy. Soc. Can. **26**:13, 1932.

parathyroid-controlled fraction and thus be retained in solution until they can be eliminated by precipitation into bone or excretion.

One other point in this work remains for discussion. It relates to the cause of the lesions seen in hypervitaminosis D rather than to the cause of the calcifications. It seems clear that the mechanism of calcification is due to a shift of calcium from the blood to the tissues. On the other hand, the lesion which may conceivably be caused by the antecedent shift of calcium from the tissues to the blood is not well known. It was suggested by Ham [4] that the withdrawal of calcium from the tissues during the upswing of the serum calcium curve in hypervitaminosis D should be considered as a possible cause of injury to the tissues. The work of McJunkin, Tweedy and Breuhaus [9] is significant in indicating the complexities of the problem concerning the causation of damage to tissue in disturbances of calcium metabolism. They indicate the lesion to be caused, not by a direct action of calcium on the tissues, but by a disturbance of the calcium content of the cells. In this connection, it should be stated that in the experiments utilizing single doses of parathyroid hormone or vitamin D there may be two different effects produced on the tissues, one due to withdrawal of calcium and the other due to precipitation of calcium. The second follows the first quite rapidly, so that one is unable to obtain by this procedure exclusive evidence of withdrawal of calcium which has been continued for a sufficient length of time to allow pathologic lesions to mature. It is obvious, however, that the evidence points to a disturbance of calcium balance between cells and tissue fluids as a potent factor in the institution of the necrosis and infiltration by inflammatory cells. It is exceedingly interesting that in rats disturbances in the metabolism of calcium can result in the production of myocardial lesions of an inflammatory type which tend to be scattered along the smaller branches of the coronary vessels.

SUMMARY

Following a single enormous dose of activated ergosterol the serum calcium level of rats was found to rise for a period of approximately two to three days and then to fall gradually.

Pathologic calcifications did not appear in these animals when the serum calcium level was rising, but appeared in large numbers when it was falling.

As the evidence from these experiments and other sources shows that there is no direct relationship between the level of the serum calcium and the production of calcifications, it is assumed that the state of the serum calcium during the rise in its level is different from its state when the level is falling.

From the evidence at hand regarding the parathyroid hormone it seems logical to assume that the rise in the serum calcium curve is

caused by the attraction of the parathyroid-controlled fraction of the serum calcium for calcium which is obtained from the intestine, bones and other tissues.

The evidence obtained in these experiments indicates the fall in the level of the serum calcium to be caused by a release of calcium from the fraction of the serum calcium controlled by the parathyroid hormone, and as this phenomenon would necessitate the maintenance of a large amount of calcium in the serum in simple solution until it could be deposited in bone or excreted, and as the serum can retain only a small amount of calcium in simple solution, precipitation occurs in the tissues.

The toxic effect of both parathyroid hormone and vitamin D in enormous doses can be explained without assuming the portion of the serum calcium associated with the parathyroid hormone to be physiologically active.

Although the calcifications of hypervitaminosis D may be explained by a shift in calcium from the blood to the tissues, it is possible that other features of the lesions, such as necrosis and infiltration by inflammatory cells, may be caused primarily by a disturbance in the calcium balance between the cells and tissue fluids. This balance conceivably is disturbed on the upswing of the serum calcium curve because of withdrawal of calcium from the tissues. Thus the cause of the calcifications may not be identical with the cause of the necrosis and infiltration by inflammatory cells.

EXPERIMENTAL INFARCTION OF THE INTERVENTRICULAR SEPTUM OF THE CANINE HEART

AN ANATOMIC AND ELECTROCARDIOGRAPHIC STUDY, WITH A NOTE ON THE NERVE TISSUE OF THE CONDUCTION SYSTEM

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Previous studies of experimental cardiac infarction have not dealt particularly with the changes in the interventricular septum. In man, a lesion in that location may cause grave disturbances in rhythm, sometimes total heart block and ventricular standstill. This is so both when the infarcts are recent [1] and when they have become organized into scars.[2] Mural thrombosis of either side of the septum, with a wide variety of sequences due to embolism, is also observed, and, while extremely rare, spontaneous perforation of the infarcted septum has been recorded.[3] The exact type of disturbance depends on the location and dimensions of the infarct as well as on its age. The present study concerns the effect of infarcts produced in the interventricular septum in the dog by ligation of the septal branch of the left coronary artery.[4] This artery was chosen because most workers agree that from it the atrioventricular node receives a large part, and the bundle of His, all, of the arterial blood supply.[5]

From the Norman Bridge Pathological Laboratory, Rush Medical College.

1. Levine, S. A., and Brown, C. L.: Medicine **8**:245, 1929.

2. (*a*) Géraudel, E., and Gautier, C.: Ann. d'anat. path. **8**:339, 1931. (*b*) Mahaim, I.: Maladies organiques du faisceau de His-Tawara, Paris, Masson & Cie, 1931.

3. Freeman, W., and Griffin, E. D.: Am. Heart J. **7**:732, 1932.

4. Throughout this paper, the term "septal artery" refers to the large branch of the left coronary artery which arises near the bifurcation of the main trunk into circumflex and anterior descending branches and penetrates the septum from in front. No attempt was made in this study to ligate the smaller, posterior branch, usually called "ramus septi fibrosi," although, as Kahn suggested in 1911, both vessels would have to be occluded to render the conduction system totally anemic.

5. (*a*) Haas, G.: Anat. Hefte **43**:627, 1911. (*b*) Kahn, R. H.: Arch. f. d. ges. Physiol. **163**:506, 1916. (*c*) Spalteholz, W.: Die Arterien der Herzwand, Leipzig, S. Hirzel, 1924. (*d*) Lauterbach, W.: Ztschr. f. d. ges. exper. Med. **61**: 665, 1928. (*e*) Moore, R. A.: Am. Heart J. **5**:743, 1930.

The existence of the dog's septal artery and the difficulties attendant on its experimental occlusion have been recognized ever since the description of it in 1881 by Cohnheim and von Schulthess-Rechberg.[6] In 1896, Porter [7] ligated this vessel in three dogs which were not allowed to recover from the anesthetic. He was chiefly interested in the controversy then taking place over the cause of ventricular standstill after ligation of the coronary arteries, and offered his experiments as part of a demonstration that the frequency and speed of cardiac arrest were proportional to the size of the artery occluded, for ligation of the septal artery, the smallest of those tied by him, did not cause the heart to stop beating.[8] Porter made no statement as to the condition of the septum following ligation of this artery.

Observations on the association of electrocardiographic changes with experiments on the septal artery were first reported by Kahn.[9] He passed a ligature around the artery and noted indications of a lesion in the bundle branches, most frequently the right, when the ligature was drawn taut. More recently, the immediate changes in the electrocardiographic tracing following ligation of the septal artery in the dog were reported by Lauterbach [5d] (1928). He produced a transitory increase in the PQ interval, followed by a partial or total block. Most typically there appeared a bundle-branch block, usually right-sided. In addition, the changes in the T wave characteristic of occlusion of a branch of the left coronary artery were noted. The experiments lasted about seven hours, and tracings were made every few minutes. Because the blood vessels in a large part of the interventricular septum were not filled with a mercuric sulphide and gelatin mixture which he injected into the coronary arteries after death, Lauterbach concluded that ischemia of the septum was the cause of the electrocardiographic changes.

For the purposes of this study, the transthoracic operative method used by Rukstinat [10] was chosen, which, by avoiding rib resection and thereby subjecting the animals to as little trauma as possible, affords a means of observing the effects of interruption of the circulation to the dog's septum after the animals recover. Medium-sized mongrels

6. Cohnheim, J., and von Schulthess-Rechberg, A.: Virchows Arch. f. path. Anat. **85**:503, 1881.

7. Porter, W. T.: J. Exper. Med. **1**:46, 1896.

8. Kahn pointed out in 1916 that Porter did not make absolutely clear which of the two arteries to the septum was tied, as the designation was simply "ramus septi." Careful reading of Porter's article indicates, however, that the artery tied was in all probability the same vessel with which the present experiments are concerned.

9. Kahn, R. H.: Arch. f. d. ges. Physiol. **140**:627, 1911.

10. Rukstinat, G. L.: J. A. M. A. **96**:26, 1931.

of even disposition were used. The operations were performed under ether anesthesia, with sterile precautions; the manner of preparation and ligation of the septal artery did not differ essentially from that described by previous observers.[11] The dogs died or were killed at intervals of from twenty minutes to three months after ligation of the artery. Death was brought about in the majority of the animals by high section of the spinal cord. In this way, the dogs died practically instantaneously, and it was usually possible to avoid the agonal changes, such as subendocardial hemorrhage, that accompany death from an overdose of ether. Observations of the rhythm of the heart beat were made by palpation and auscultation, and, when possible, with the electrocardiograph. After death, the brain and the organs of the chest and abdomen were examined.

The operation is difficult, and a number of dogs died of hemorrhage while still anesthetized. In others surviving, the ligature had not been placed about the artery, and infarction of the intraventricular septum had not occurred. However, in twelve dogs, conditions were obtained suitable for study; i. e., the septal artery had been occluded either wholly or in part, and infarction of the interventricular septum of greater or less degree had followed.

Classified according to the degree of occlusion of the septal artery, the twelve experiments fell naturally into four groups (table).

Unique among the experiments was that on dog 1, which constitutes the first group. Ligation of the septal artery was followed by marked dilatation and cyanosis of the heart, which stopped beating twenty minutes after the ligature had been tied. Only microscopic changes were found in the septum. These consisted chiefly in an engorgement of the veins with blood. It is not possible to decide with certainty just how much influence the cutting off of the blood supply to the septum had in producing death, for two other dogs died on the operating table with the same signs of cyanosis and cardiac dilatation, without any ligation having taken place, and in one of them there was difficulty with the artificial respiration.

Six experiments [12] in which the septal artery was completely occluded by the ligature, and in which the lesion that came to be recognized as a typical infarct was produced, form group 2 (dogs 2 to 7 inclusive, in the table). The infarct was always extensive on the left ventricular surface of the septum, occupying from one fourth to three fourths of that surface. The changed region extended from the attached margins

11. Kahn.[5b] Lauterbach.[5d] Kahn.[9]

12. The first four of these were reported briefly in a preliminary statement read at the meeting of the Illinois section of the Society for Experimental Biology and Medicine in February, 1932 (Proc. Soc. Exper. Biol. & Med. **30**:15, 1932).

Summary of Experiments

Experiments	Dog	Time Between Operation and Death	Condition of Septal Artery	Change in Septum	Approximate Fraction of Auriculoventricular Node Infarcted	Postoperative Electrocardiographic Notes	Complications	Mode of Death
Group 1	1	20 min.	Occluded by ligature	Veins engorged with blood	Undetermined	No tracings	Cardiac dilatation ending in death	Spontaneous
Group 2	2	66 days	Occluded by ligature	Infarct	Undetermined	No tracings	None	Ether
	3	11 days	Occluded by ligature	Infarct	One seventh	Regular sinus rhythm	Emaciation; bronchopneumonia	Spontaneous
	4	5 days	Occluded by ligature	Infarct	Undetermined	No tracings	Suppuration of wound	Spontaneous
	5	6 days	Occluded by ligature	Infarct	One third	Tachycardia; regular sinus rhythm	Suppuration of wound	High section of spinal cord
	6	7 days	Occluded by ligature	Infarct	One half	Tachycardia; transient complete heart block	Suppuration of wound	High section of spinal cord
	7	42 days	Double; one branch occluded by ligature	Infarct	No change	Tachycardia; extrasystoles	Suppuration of wound; pyopneumothorax; recovery	High section of spinal cord
Group 3	8	52 days	Narrowed by ligature	Microscopic hemorrhage and necrosis	Undetermined	Regular sinus rhythm	Distemper; recovery; emaciation	High section of spinal cord
	9	90 days	Almost completely occluded by ligature	Infarct	One twentieth	Tachycardia; regular sinus rhythm	None	High section of spinal cord
	10	3 days	Not included in knot; narrowed from without	Small, atypical infarct	One tenth	Regular sinus rhythm	Suppuration of wound	High section of spinal cord
Group 4	11	5 or 6 days	Surrounded by ligature but patent	Microscopic necrosis	No change	Regular sinus rhythm	Suppuration of wound	Spontaneous
	12	3 days	Patent	Infarct	No change	Regular sinus rhythm	Suppuration of wound; infarct of outer wall of left ventricle	Spontaneous

of the aortic cusps toward the apex of the left ventricle. The widest portion of the infarct was usually a short distance below the aortic ring. The edges were well defined and jagged (figs. 1 and 2*A*).

In two hearts (dogs 6 and 7) both surfaces of the septum were correspondingly altered (fig. 2*B*); in two others (dogs 2 and 4) the gross change on the right side of the septum was slight; in the remaining two of this group there was no noteworthy gross alteration of the surface of the right side of the septum.

Fig. 1 (dog 2).—The infarcted left side of the interventricular septum is shown. The lesion extends from the aortic ring toward the apex of the heart and is typical of the position of the infarcts caused by ligation of the septal artery. The specimen was fixed in Kaiserling's solution.

In all six hearts, the endocardium was intact on both sides of the septum; indeed, the bands of Purkinje's fibers, gray against the darker infarcted muscle beneath them, were vivid and easily followed because the endocardium was so normally translucent.

Microscopically, the alterations in the interventricular septum were chiefly confined to the muscle. The stages of infarction varied from the acute changes in the hearts of dogs 4, 5 and 6, which had lived less than a week after the operation, to the later stages of organization and repair present in dog 3 (eleven days) and in dog 7 (fifty-nine days). The protocols should be consulted for details of these lesions. Suffice

it to say here that the alterations were usually consistent with the gross appearance.

In the third group of experiments (dogs 8, 9 and 10), the channels of the septal arteries were found incompletely obliterated at the site of ligation, and the infarcts in two of the septums were small and not in the usual location. The lesion of dog 9, however, was in all particulars like the lesions in the dogs of group 2. Since the septal arteries of dogs

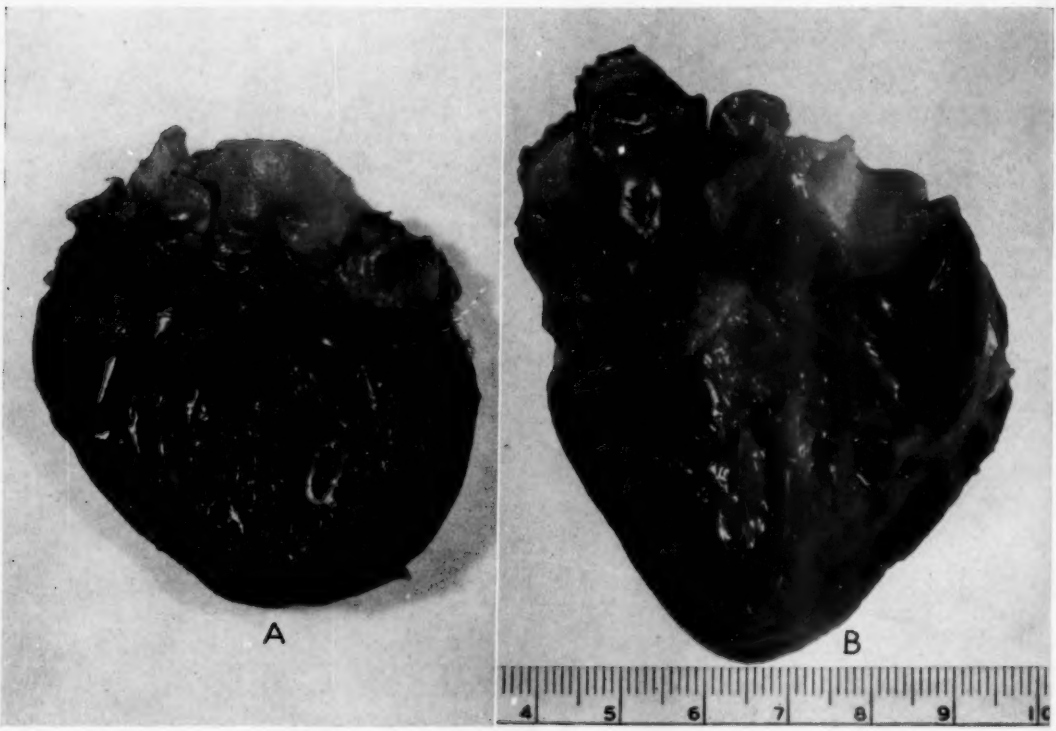

Fig. 2 (dogs 3 and 7).—*A*, the heart of dog 3; unfixed specimen. The photograph was taken on a slant; hence the gray region of infarction below the aortic cusps appears relatively smaller than it actually was. The electrocardiogram of this dog is pictured in figure 5 *A*. *B*, the right side of the septum of dog 7; unfixed specimen. The lesion is to the right of the reflected tricuspid leaflet and involves the base of the papillary muscles. In the changed region, the septal wall is noticeably thinned. For the corresponding electrocardiograms see figure 6.

8 and 9 were completely surrounded by the ligating thread when examined after death, it is possible either that the arteries were incompletely occluded at the time of operation, or that recanalization took place subsequently. The acute inflammatory reaction about the operative field

probably accounts for the narrowing of the septal artery of dog 10, for the ligature did not surround the artery.

In the fourth group are two experiments (dogs 11 and 12) in which the septal arteries were patent at the time of the postmortem examination. The changes in the septum of dog 11 were microscopic, but the lesion in dog 12 was extensive and involved the outer wall of the left ventricle as well as the septum. In both dogs, inflammation in the wound, in addition to the trauma of the operative manipulations, must have caused temporary occlusion of the septal artery, of sufficient duration to produce the lesions.

NERVE TISSUE IN THE CONDUCTION SYSTEM

In the microscopic examination of the conduction systems of these dogs, a special study was made of the nerves and ganglion cells associated with the specialized muscle tissue.

The anatomic relations of the ganglion cells in the conduction system have been described by so few observers [13] that a preliminary study was made to establish the normal conditions. Six hearts were removed from apparently normal and lively dogs after the animals had been killed by an overdose of ether. The right and left ventricular and auricular walls of the lateral sides were cut away, leaving only the interventricular and interauricular septum. The block containing the structures pertinent to this study was removed by making four cuts along the following lines: one, in the vertical axis of the heart 4 mm. anterior to the coronary sinus; a second, parallel to the first, through the middle of the anterior tricuspid leaflet; a third, parallel with the tricuspid ring and 2 mm. below it, and a fourth, parallel with the third, 1 cm. above the ring. This block was sliced into sections from 1 to 2 mm. thick by cuts parallel to the long axis of the heart, and these sections were stained with intravital methylene blue according to a modification of the immersion technic of Wilson.[14]

Microscopic sections were cut to about 10 microns. In addition, a number of sections from each heart were destained of methylene blue by creosote and restained with hematoxylin and eosin.

The conditions were essentially the same in all the hearts. Numerous nerve trunks, taking a deep blue stain and readily differentiated from

13. Wilson, J. G.: Proc. Roy. Soc., London **81**:151, 1909. DeWitt, L.: Anat. Rec. **3**:475, 1909.

14. This method differed from that of Wilson in that absolute instead of 95 per cent alcohol was used for dehydration, and that embedding was in a concentrated preparation of pyroxylin (celloidin) instead of paraffin. It was found early in the work that the dye was leached from the tissues by the more dilute alcohol, even after they had been embedded in the pyroxylin.

connective tissue bundles by the nodules of the nerve fibers, were found throughout the region from the coronary sinus to the commissure of the medial and anterior tricuspid leaflets and from the auriculoventricular fibrous septum to about 1 cm. above the tricuspid ring. The nerves varied from fine fibrils to very coarse trunks and differed greatly in the intensity with which they took the methylene blue. Small nerve fibers were found entering muscle cells. Throughout the region occupied by nerves were numerous separate ganglion cells and many ganglion cell groups, lying in the adipose tissue between the specialized muscle cells. The number of ganglion cells in each group varied from five to more than one hundred. The largest groups of ganglion cells lay about the middle of the block or about from 1 to 1.5 cm. from the coronary sinus and 0.5 cm. above the fibrous auriculoventricular septum. Some of the groups lay along large trunks (fig. 3*A*), while nerve trunks led from others. There were a few individual ganglion cells along the course of the nerve trunks; others were isolated. Toward the lower end of the atrioventricular node the ganglion cell groups diminished in size and number. The majority of the ganglion cells were multipolar (fig. 3*B*), and each was surrounded by a thin endothelial capsule. The nucleus was large and round or oval, and stained deeply with methylene blue. However, in every group there were a few ganglion cells which did not stain with methylene blue.

In sections stained with hematoxylin and eosin, the ganglion cells were not so pronounced as in those stained with methylene blue, but the nuclei were deep purple, and the cytoplasm was light pink. The cell processes were visible but indistinct. The capsules about the ganglion cells were formed of long, thin, flat cells.

The same method being used, one human heart was examined, which was obtained six hours after the death of a patient from bullet wounds. One group of five ganglion cells was found about 1 cm. from the coronary sinus and about 0.5 cm. above the auriculoventricular fibrous septum. The cells were similar to those found in the dog's heart, except that they were slightly smaller. In addition to the group, several discrete ganglion cells were scattered throughout the node. Nerve trunks were numerous and similar in all respects to those in the dog's heart.

Heretofore observers have dealt mainly with the conduction systems of animals others than dogs and man, in regard to the nerve tissue there, although it has been studied in both species. The reports lead one to believe that ganglion cells, nerves and nerve trunks are scarce in the hearts of these animals. The results of the foregoing studies indicate that the contrary is the case. The matter resolves itself into one of patient and diligent searching, from which it must be conceded

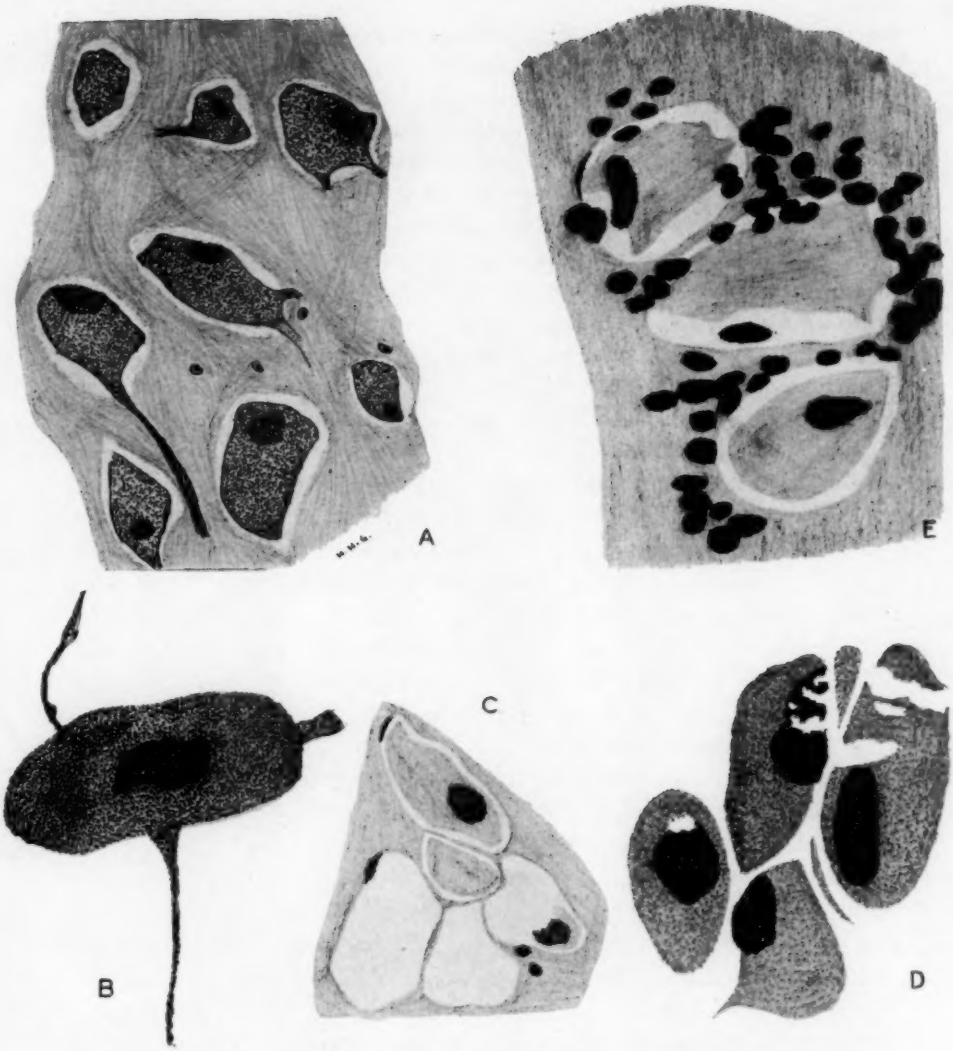

Fig. 3.—*A*, ganglion cell group in the auriculoventricular node of a normal dog; intravital methylene blue. The group is traversed by a nerve trunk. *B*, a typical multipolar ganglion cell in the auriculoventricular node of a normal dog; intravital methylene blue. *C*, part of a ganglion cell group in the auriculoventricular node of a dog following infarction of the interventricular septum; hematoxylin and eosin. Note the absence of some ganglion cells from their endothelial capsules and the fragmentation of one cell. *D*, fragmentation of ganglion cells in part of a group in the auriculoventricular node of a dog following infarction of the interventricular septum; intravital methylene blue. *E*, portion of a ganglion cell group infiltrated by leukocytes following extensive infarction of the interventricular septum; intravital methylene blue. The cytoplasm of the leukocytes is practically indistinguishable. See the protocol of dog 6 and the electrocardiograms in figure 4.

that nerves, nerve trunks and ganglion cells are prominent in the dog's conduction system and less so in that of man.

For demonstrating nerves and ganglion cells, the same method that had been used in the work on normal dogs' hearts was then applied to the hearts of eight animals in which ligation of the septal branch of the left coronary artery had brought about infarction of the interventricular septum. In five of the eight infarcted hearts, the ganglion cells of the conduction system were unaltered, in two slightly altered, and in one markedly so. The changes were essentially of the same type, differing only in degree. Many ganglion cells were absent from their endothelial capsules (fig. 3*C*). Others failed to stain with methylene blue, although they could be distinguished because of a network of nuclear material. In one heart the nuclei were pyknotic, there was fragmentation with extrusion of the nuclei (fig. 3*D*), and infiltration by leukocytes was seen in some of the ganglion cell groups (fig. 3*E*).

It was considerably more difficult to find ganglion cells in the three hearts in which they had been altered than in the other hearts. This was true whether the sections were stained with methylene blue or with hematoxylin and eosin.

Sections of the atrioventricular nodes of nine dogs were stained with hematoxylin and eosin. In four (dogs 7, 8, 11 and 12), the nodal tissue was unchanged. The fraction of changed tissue in other nodes was approximately as follows: dog 9, one twentieth; dog 10, one tenth; dog 3, one seventh; dog 5, one third; dog 6, one half. There was no close parallel between the changes in the nodes recognized as infarcts and the changes found in ganglion cells.

ELECTROCARDIOGRAMS

Electrocardiograms were used in this study for the purpose of demonstrating changes in the cardiac rhythm that might conceivably be the sequence of ligation of the septal artery. As noted, such changes occurred in the acute experiments of Lauterbach.[5d] The results of the present experiments in this regard are summarized in the table.

Electrocardiograms were not made for dogs 1, 2 and 4. Tracings for dogs 3 and 6 were made only after operation. The records of all the other dogs include electrocardiograms made before operation as well. The shortest interval between operation and tracing was nine hours; the longest, twenty days. When feasible, a final tracing was made as near the time of postmortem examination as possible. All tracings were made with the dogs in the dorsal position and without anesthesia or sedatives of any kind. Dr. C. J. Lundy contributed much assistance and counsel in recording and interpreting the electrocardiograms.

There was a striking similarity in the changes in the electrocardiograms following operation in two particulars. First, the immediate effect on the rate was an increase often up to double that present in tracings made before ligation. Second, the changes, with one exception, had little or no relation to heart block. The one exception was the first postoperative tracing for dog 6 (fig. 4), made twenty-four hours after operation. In it the auricular waves were completely dissociated from the ventricular complexes. Subsequently, the normal relationships were resumed.

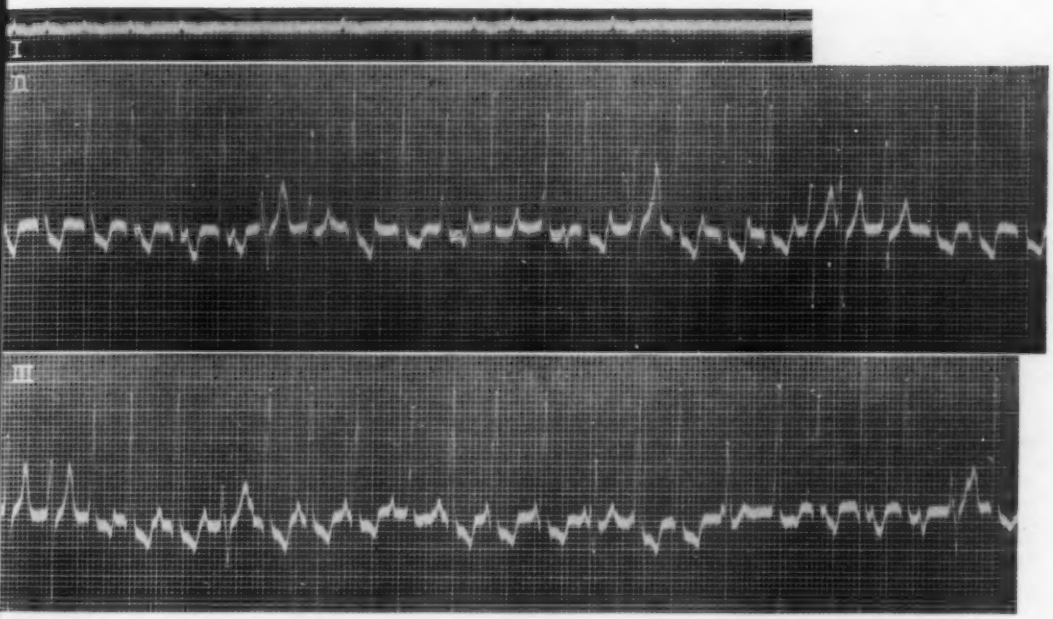

Fig. 4 (dog 6).—Electrocardiogram taken twenty-four hours after operation. It records complete auriculoventricular dissociation; auricular rate, 176; ventricular rate, 200; QRS, from 0.05 to 0.10 second. There is shown a combination of complete heart block, auricular and ventricular tachycardia and many ventricular extrasystoles.

A frequent alteration noted in the configuration of the T wave is that seen in the tracings for dogs 6, 7 and 9 (figs. 5 *D* and *F* and 6*C*), a change considered by some authorities characteristic of occlusion of a branch of the left coronary artery.[15]

In correlating the anatomic changes in these experiments with the electrocardiograms, one is impressed with the fact that, although the artery presumably carrying the major portion of the blood supply to

15. Pardee, H. E. B.: Am. J. M. Sc. **169**:270, 1925.

the conduction system was occluded sufficiently to cause infarction of a large portion of the septum between the ventricles, lasting heart block of any sort did not result. The most profoundly altered electrocardiogram, the only tracing in which there was demonstrated for a while at least complete heart block, was that for the dog in which the septum and auriculoventricular node showed the greatest amount of change (dog 6, fig. 4). Perhaps if tracings had been made sooner after operation than was usual in this study, heart block, even though transient, might have been recorded more frequently. But the bizarre tracing for dog 7, made nine hours after ligation of the septal artery, illustrates that this is not necessarily the case. In it there are shown marked tachy-

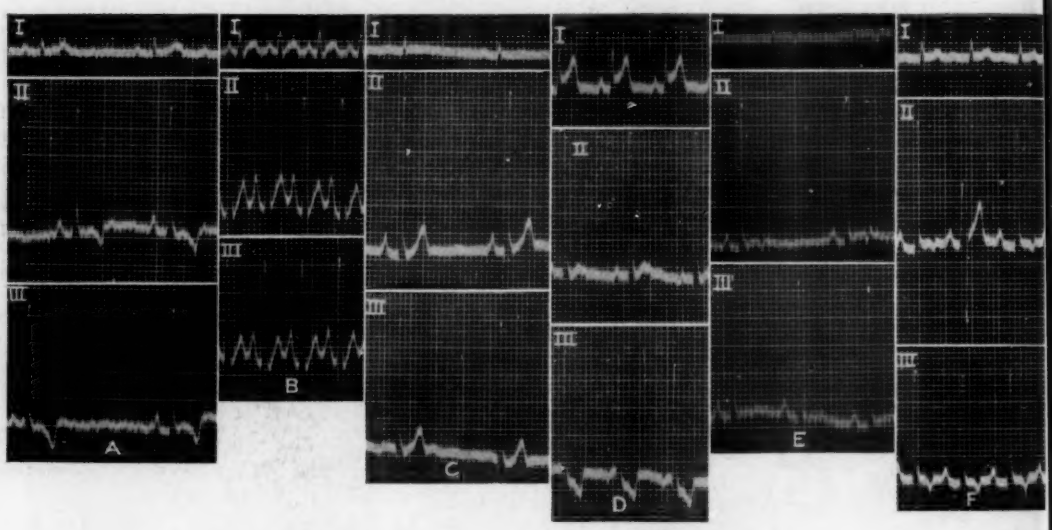

Fig. 5 (dogs 3, 5, 6 and 9).—*A*, electrocardiogram of dog 3 ten days after operation: cardiac rate, 75; PR, 0.12 second; QRS, 0.06 second; $T_{2,3}$, inverted. No evidence of auriculoventricular dissociation. *B*, electrocardiogram of dog 5 five days after operation: cardiac rate, 214; regular sinus rhythm; PR, 0.10 second; QRS, 0.06 second. The rate is more than double that recorded before operation, while the PR interval is the same. This suggests a possible delay in auriculoventricular conduction, but cannot be accepted as good evidence. *C*, electrocardiogram of dog 9 before operation: cardiac rate, 83; sinus arrhythmia; PR, from 0.12 to 0.16 second; QRS, 0.06. Note height of $T_{2,3}$. *D*, electrocardiogram of dog 9 five days after operation: cardiac rate, 145; regular sinus rhythm; PR, 0.10 second; QRS, 0.06 second; ST^1, markedly elevated; ST_3, depressed; T_3, inverted. *E*, electrocardiogram of dog 6 before operation: cardiac rate, 93; sinus arrhythmia; PR, 0.12 second; QRS, 0.05 second; somatic tremor. *F*, electrocardiogram of dog 6 four days after operation: cardiac rate, 170; occasional ventricular extrasystole; PR, 9.14 second; QRS, 0.06 second; $ST_{1,2,3}$, elevated; $T_{2,3}$, inverted. The smallest vertical divisions of the graphs represent 0.04 second. White dots indicate the limit of excursion.

cardia and a profusion of extrasystoles, but no sign of atrioventricular dissociation [16] (fig. 6*B*).

There seemed to be nothing in the alterations of most of the tracings which could be considered a specific indication of the presence of the septal infarct. It was not possible to predict correctly the presence or the absence of an infarcted septum by examining the electrocardiograms, with the one exception (dog 6) noted in a foregoing paragraph, in which complete dissociation was so striking.

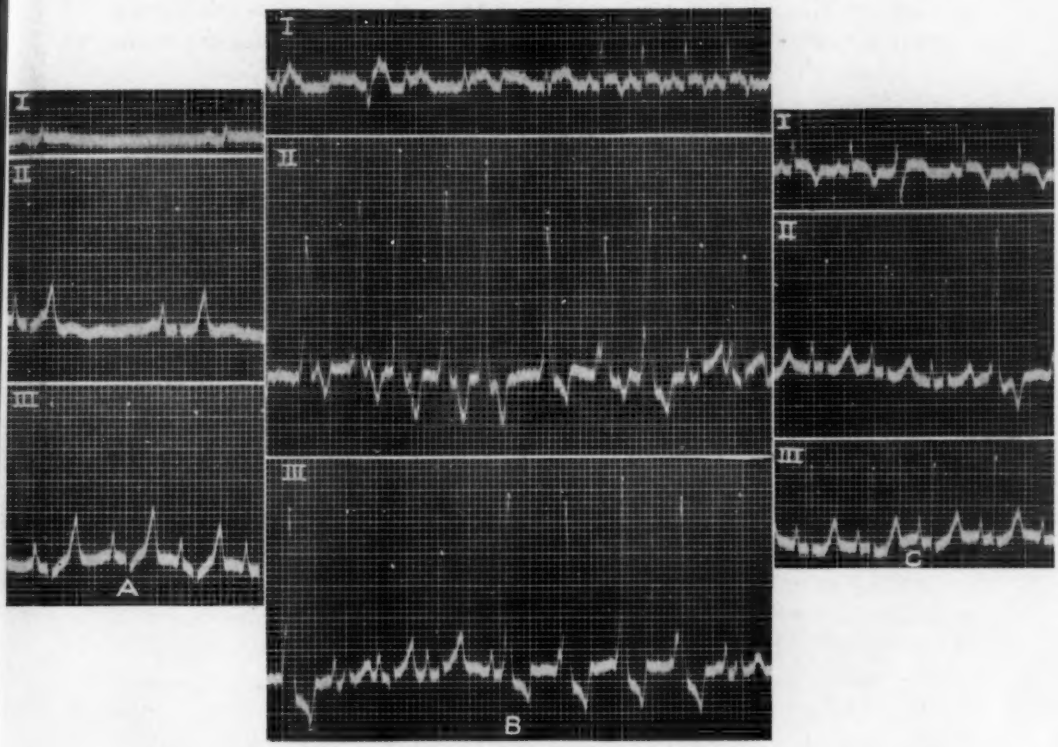

Fig. 6 (dog 7).—*A*, electrocardiogram taken before operation: cardiac rate, 80; sinus arrhythmia; PR, from 0.08 to 0.10 second; QRS, 0.04 second. Note height of T_{II}. *B*, electrocardiogram taken nine hours after operation: cardiac rate, 190; PR, 0.08 second; QRS, 0.04 second; many ventricular extrasystoles, no heart block. *C*, electrocardiogram taken twenty-four hours after operation: cardiac rate, 170: PR, 0.09 second; QRS, 0.04 second; ST_1, elevated; T_1, inverted; occasional extrasystoles.

Neither was there a constant relationship between the electrocardiographic changes and the alterations in the ganglion cells of the conduction

16. Post mortem, the septal artery was found to be double, only one of the branches having been occluded.

system. True, the ganglion cells of dog 6 suffered the most damage of all, and the animal had a transient heart block. If one assumes that the ischemia produced retrogressive changes in the node from which the sensitive ganglion cells were unable to recover, whereas similar changes were slight or reversible in enough of the hardier Purkinje fibers to allow conduction eventually to proceed, one is tempted to infer that the ganglion cells are, therefore, not primarily concerned with the mechanism of the conduction of the cardiac impulse.

The reversible nature of the phenomenon of block has been emphasized by Kisch [17] in his experiments on the action of perfused isolated canine hearts. Before perfusing the heart, he had clamped off the left coronary artery at its origin in order to shut off the circulation to the conduction system from both front and rear septal arteries. When perfusion was well under way, with the auricles beating from thirty to fifty-five times and the ventricles once per minute, the obstruction was removed from the left coronary artery, and the right coronary artery was clamped. The auricular and ventricular beats then assumed their normal relationship to each other. Release of the right coronary artery and reclamping of the left then produced a gradually increasing interference in conduction which, within four minutes, resulted in complete auriculoventricular dissociation.

It is probable that in the experiments of Lauterbach,[5d] which have been referred to, the heart block produced was of the same transitory nature as in our experiments, and would have disappeared with the passage of time had his dogs lived.

That tachycardia frequently follows coronary occlusion, both experimental and otherwise, is well known, but as far as we are aware, previous observers have not paid particular attention to the effects of infarcts produced by interruption of the circulation to the conduction system specifically. It would seem that the results of the infarcts produced in the present experiments point to the irritative type of lesion recently stressed by Mahaim.[2b] Hyperexcitability was evidenced by the tachycardia and premature contractions. The reason more frequent or more permanent heart block did not occur is probably that the circulation of blood to the septum from behind was usually adequate to prevent interruption of the continuity of the His-Tawara system.

PROTOCOLS

Dog 1.—After ligation of the septal artery, the heart became cyanotic, dilated, and stopped beating while the chest was being closed, twenty minutes after the artery had been tied. The ligature was found tight around the septal artery. There was no noteworthy gross alteration of the myocardium. Microscopically, the small veins were engorged with blood.

17. Kisch, B.: Deutsches Arch. f. klin. Med. **135**:281, 1921.

Dog 2.—Recovery from the operation was uneventful. The heart beat was regular, the rate on one occasion being 120 per minute. Six weeks after operation, as the dog had become emaciated and weak, and refused food, it was killed by an overdose of ether. The septal artery was found occluded, and there was an infarct in the interventricular septum occupying four fifths of the left and less than one tenth of the right side, composed largely of fibrous tissue (fig. 1).

Dog 3.—Following the operation, the dog recovered well, and there was no cardiac irregularity. On the tenth day, it became weak and refused food, and tremors of the extremities developed. An electrocardiogram was made in which there was no sign of auriculoventricular dissociation (fig. 5 *A*). The following day, the eleventh since the ligation of the septal artery, the animal died spontaneously.

There was an infarct, already partly organized into fibrous tissue, occupying one fourth of the left side of the interventricular septum (fig. 2 *A*). Microscopically, about one seventh of the Purkinje tissue of the auriculoventricular node was similarly altered.

Death was apparently due to bronchopneumonia, evidence of which was abundant in both lungs.

Dog 4.—During the operation, the fifth rib was accidentally fractured. The postoperative course was stormy owing to infection in the wound, and the dog died on the fifth day without evidence of cardiac irregularity. No electrocardiogram was made.

The infarct in the interventricular septum was a spatula-shaped region of friable, yellow tissue occupying the middle of the left surface and a smaller portion of the right. On the left side, the upper margin of the lesion was at the aortic ring. The microscopic changes were those of coagulation necrosis, hemorrhage and leukocytic infiltration.

The left lung had been pierced by the rough end of the broken rib, and there was a fibrinopurulent exudate in the left pleural cavity and the pericardial sac.

Dog 5.—The heart rate as recorded by electrocardiogram before operation was 100 per minute. Immediately following ligation of the septal artery, the heart dilated so that it was impossible to close the pericardial sac. Three days later the pulse was 160 per minute and regular. In an electrocardiogram taken on the sixth day, the rate was recorded as 214 per minute and the rhythm was shown to be regular (fig. 5 *B*). Because of suppuration of the wound, the dog was then killed by high section of the spinal cord under anesthesia.

There were two arteries of unequal size at the usual location of the septal artery. Only the larger was occluded by the ligature. The infarct occupied one third of the left side of the septum. Over the infarcted muscle the left branch of the bundle of His was plainly visible through the smooth, transparent endocardium. Microscopically, about one third of the auriculoventricular node was infarcted.

Dog 6.—Although the anesthesia was not excessively deep, the heart dilated during the preliminary dissection of the coronary arteries, and the left ventricle stopped beating. The region of the sino-auricular node was massaged briefly, and the heart again beat naturally. The septal artery was ligated without further event. The first electrocardiogram was made twenty-four hours later. In it there was demonstrated complete atrioventricular dissociation (fig. 4). During the next six days, two tracings were made in which there was no indication of block (fig. 5 *F*). Because of infection in the wound, the dog was killed by high section of the spinal cord seven days after operation.

There were left fibrinopurulent pleuritis and mediastinitis. A large infarct involved three fourths of the left side of the interventricular septum and an equal amount of the right side. The endocardium was shiny and transparent. The course of the branches of the bundle of His was faint. The entire thickness of the septum was infarcted. Microscopically, about one half of the auriculoventricular node had been similarly changed, and the ganglion cells in it were altered by marked retrogressive changes and leukocytic infiltration (fig. 3 *E*).

Dog 7.—There was nothing unusual of importance noted during the ligation of the septal artery. An electrocardiogram made nine hours later recorded many extrasystoles, and the cardiac rate was more than double that before operation (fig. 6 *A* and *B*). In subsequent tracings made twenty-four and forty-five hours after ligation, the premature contractions diminished in number and then disappeared, but the rate remained rapid (fig. 6 *C*). During the first week, there was some drainage from the incision, but otherwise the wound healed well, and the dog lived uneventfully with a normal cardiac rate and rhythm till the fifty-ninth day after operation, when death was produced by high section of the spinal cord under ether anesthesia.

The septum was thinned in a region of old infarction 3 by 1 cm. involving from one fourth to one third of its muscle (fig. 2 *B*). The septal artery was double; one branch only had been ligated. Microscopically, the septal infarct contained fibrous tissue; no change was found in the Purkinje fibers of the auriculoventricular node.

Dog 8.—During the first week after operation, the dog evinced weakness, lassitude and loss of appetite and had a caking discharge from the nose and eyes. However, it recovered from this distemper and again became vigorous. Electrocardiograms were made twenty and fifty-one days after operation. There was no alteration in the rate or rhythm of the heart. Six or seven weeks after operation, the dog lost its appetite, and tremors, spasticity of the extremities and extreme weakness gradually developed. It was killed on the fifty-second day by high section of the spinal cord under ether anesthesia. The diaphragm continued to contract and the heart to beat after the limbs were flaccid. The cardiac contractions were regular and appeared normal.

The ligature was found to surround the septal artery completely; the arterial channel had been narrowed so as to admit only a fine broom-straw. There was no infarct visible grossly in the septum, but there was histologic evidence of diffuse scarring and fresh hemorrhage. There were extensive fatty changes in the liver. The lungs and brain were not remarkable.

Dog 9.—The first postoperative electrocardiogram was made on the fifth day. The rate was almost double; there was no heart block (fig. 5 *C* and *D*). During the next eleven weeks, the dog's condition was good. Electrocardiograms were made seven and twelve weeks after operation. In the first of these, one ventricular extrasystole was recorded. The animal was killed three months after operation by high section of the spinal cord under ether anesthesia.

The infarct in the septum was a depressed, spatulate, fibrous scar extending from the aortic ring to within 1 cm. of the apex of the left ventricle. It occupied one third of the left surface of the septum and extended into the muscle one fourth of the width of the septal wall. The septal artery was narrowed by the ligature to a channel which allowed the passage of a coarse bristle. Distal to the annulation, the lumen of the artery was of normal width and the lining unaltered. Microscopically, about one twentieth of the auriculoventricular node was scarred.

Dog 10.—The septal artery was not seen during the operation; the ligation was made blindly. Because of infection in the wound, the dog was killed, while anesthetized, the third day after operation. The chief changes recorded in an electrocardiogram made just before death were tachycardia and an elevated ST interval.

There were extensive left serofibrinous pleuritis and pericarditis. The septal artery was not included in the silk knot, which lay close by, to the right of the left anterior descending branch. The channel of the septal artery, however, 3 mm. from its mouth was narrowed to a diameter of less than 1 mm. On the left side of the septum, there were four well defined infarcts, the largest, 10 by 13 mm. and extending through the septal wall. Both right and left branches of the bundle of His were plainly visible under the transparent endocardium. In the outer wall of the left ventricle, near the site of operation, the muscle was dead in a region 7 by 5 mm. Microscopically, in the infarcted regions, there were coagulation necrosis, hemorrhage and leukocytic infiltration. About one tenth of the auriculoventricular node was infarcted.

Dog 11.—The heart beat regularly and rapidly on the day following the operation. On the fourth day, the rate recorded by electrocardiogram was 136 per minute. There was no noteworthy change of the rhythm. The incision was intact, and the dog appeared in good condition. On the sixth day, it was found dead.

There was an abundant fibrinopurulent exudate in the left pleural cavity compressing the left lung. In the right pleural cavity was about 50 cc. of cloudy, watery liquid. The right lung was soggy with dark red blood; the liver also was bloody. Fibrin joined the visceral to the parietal pericardium about the operative field. The septal artery was completely surrounded by the silk ligature, but its lumen was uncompromised. No gross change was observed in the interventricular septum. In histologic sections of the middle of the septum, there were scattered regions of necrosis and hemorrhage. There was no change in the auriculoventricular node.

Dog 12.—The septal artery was not seen during the operation; the ligation was attempted by passing the thread blindly under the trunk of the left coronary artery near its bifurcation into descending and circumflex branches. Twenty-eight hours after the operation, the rate as recorded by electrocardiogram was 115 per minute, the rhythm regular. On the fourth day, the dog was found dead.

There were left fibrinous pleuritis and pericarditis. The septal artery was unobstructed; its exact relation to the silk knot could not be determined. Grossly, the septal infarct was a well defined truncated cone, reaching from the aortic cusps 2.7 cm. toward the apex of the left ventricle, and extending half way through the wall of the interventricular septum. The bases of both papillary muscles were infarcted, and there was an infarct a few millimeters square near the base of the tricuspid leaflets. The most conspicuous histologic changes were fragmentation of the muscle fibers and hemorrhage between the muscle bundles. There was no change in the auriculoventricular node. Passive hyperemia of the lungs, liver and kidneys was marked.

SUMMARY AND CONCLUSION

Nerve trunks, nerve fibers, groups of ganglion cells and individual ganglion cells are abundant throughout the auriculoventricular node of the dog's heart, and are present to a less degree in the node of man.

When the front septal branch of the left coronary artery of the dog was occluded by ligation and when the animals had recovered from the

immediate effects of the operation, a typical infarct was produced in the interventricular septum, and usually in part of the auriculoventricular node as well. Some of the ganglion cells and ganglion cell groups in such infarcted nodes had undergone degenerative changes.

No permanent interruption of conduction as a result of these lesions was discoverable by electrocardiograms. Mural thrombosis of the cavities of the heart was not observed. Among the possible reasons for the paucity of conduction disturbances are the richness and the variability in the arterial blood supply to the conduction system of the dog and the frequency with which the endocardium and the Purkinje fibers over the infarcts were found intact.

RELATIONSHIP BETWEEN TRAUMA SUSTAINED AT BIRTH AND ENCEPHALITIS IN CHILDREN

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In the experience of most pathologists there appear from time to time cases of encephalitis in children which are not associated with acute general infections or well established forms of encephalitis and for which the etiology remains obscure. In the literature the cases are classified as encephalitis of idiopathic origin (Brain, Hunter and Turnbull,[1] Stooss,[2] Kemkes and Saenger,[3] Low,[4] Citron, Seidmann and Zappert,[5] Eckstein[6]), as atypical forms of encephalitis (Wilckens,[7] Stern,[8] Weimann,[9] Eckstein,[6] Citron, Seidmann and Zappert[5]), as insidious encephalitis (Guillain[10]) and as encephalitis following pyogenic infections (Grinker and Stone[11]). In many of these cases the location of the lesion, the fatty changes and the cortical atrophy usually associated with paralysis cannot be wholly explained by the infection (Spielmeyer,[12] Stern[8]). One must then seek for some other underlying pathologic process. This is accomplished only with great difficulty, in that the reactions of the parenchyma of the brain and the perivascular connective tissue to inflammatory, toxic and traumatic irritants are similar and at times impossible to differentiate. Coupled with this handicap is the fact that there is no definite way of determining the age of a lesion in the brain.

Many authors explain the idiopathic types of encephalitis on a congenital or hereditary basis, a poor endowment resulting in a susceptibility

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of the substance of the brain to infections and intoxications. That some children are more susceptible to cerebral involvement than others there can be no doubt. That hereditary and congenital factors play a rôle is also plausible. The susceptibility more probably results from the injuries of the brain inevitable to the vicissitudes of labor.

In the three cases to be described, which occurred in one family, the relation of injuries sustained at birth to encephalitis was demonstrated.

REPORT OF CASES

CASE 1.—A colored boy, aged 2 years, was admitted to the pediatric service because of convulsive seizures and vomiting of two days' duration. The former was manifested by spasms of the arms, culminating in attempts to tear his face or to attack any one within reach. He never lost consciousness and recovered promptly. In the last few days he had vomited, but the exact nature of the vomiting could not be ascertained.

The past history revealed that the child had been hospitalized four months before for nervousness and vomiting. At that time no definite diagnosis was made, the central nervous system not being considered.

The child was one of twins who had been delivered at home. The birth history will be considered later.

The patient was fairly well nourished; he exhibited purposeless movements and appeared listless. The temperature was 100 F.; the pulse rate, 110 per minute. The neck was rigid; there was a positive Brudzinski sign. There was impairment of resonance in the bases of both lungs; the spleen was slightly palpable, and there was a generalized lymphadenopathy.

The spinal fluid was under moderately increased pressure; it was clear, and gave a negative reaction to the Pandy test. The cell count was 40 per cubic millimeter, of which 58 per cent were lymphocytes. The Wassermann reaction of the spinal fluid was negative. The white blood count was 9,600 per cubic millimeter; the hemoglobin was 70 per cent. A differential count revealed 54 per cent polymorphonuclear leukocytes, 38 per cent lymphocytes, 5 per cent eosinophils and 3 per cent monocytes. Urinalysis gave negative results, and the Pirquet reaction was positive.

The diagnosis was not certain. Encephalitis and tuberculous meningitis were considered.

During the short stay in the hospital (seven days), the child was persistently semiconscious.

The thymus weighed 10 Gm.; it was a light purple-gray and parenchymatous. The heart weighed 50 Gm.; the chambers were dilated, and the myocardium was soft and friable. The lungs were distended, with focal areas of atelectasis in the lower lobe of the right lung. The spleen weighed 20 Gm.; the upper pole was adherent to the diaphragm. The pulp was purple-gray and friable; follicles and trabeculae were distinct. The liver weighed 370 Gm.; it was yellowish brown and had obscure markings. The peribronchial, peritracheal, mesenteric, peripancreatic and axillary lymph nodes were uniformly enlarged to 10 mm. in diameter, soft and grayish pink.

The essential changes were in the brain. The weight was 935 Gm. The leptomeninges were thin and slightly injected and were separated by an increased

amount of fluid. The consistency of the brain was firm, and the gyri, especially those of the frontal lobes, were narrower than normal. The general appearance of the brain resembled a formaldehyde-fixed organ.

Microscopic Changes in the Brain.—In the frontal lobe, the leptomeninges over the convexity were thickened by fibrous tissue and infiltrated by loosely scattered polymorphonuclear leukocytes and round cells. The subarachnoid space over the gyri was obliterated, and often the pia seemed to fuse with the subpial portions of the cerebral cortex. In the region of the sulci, the subarachnoid space was wide,

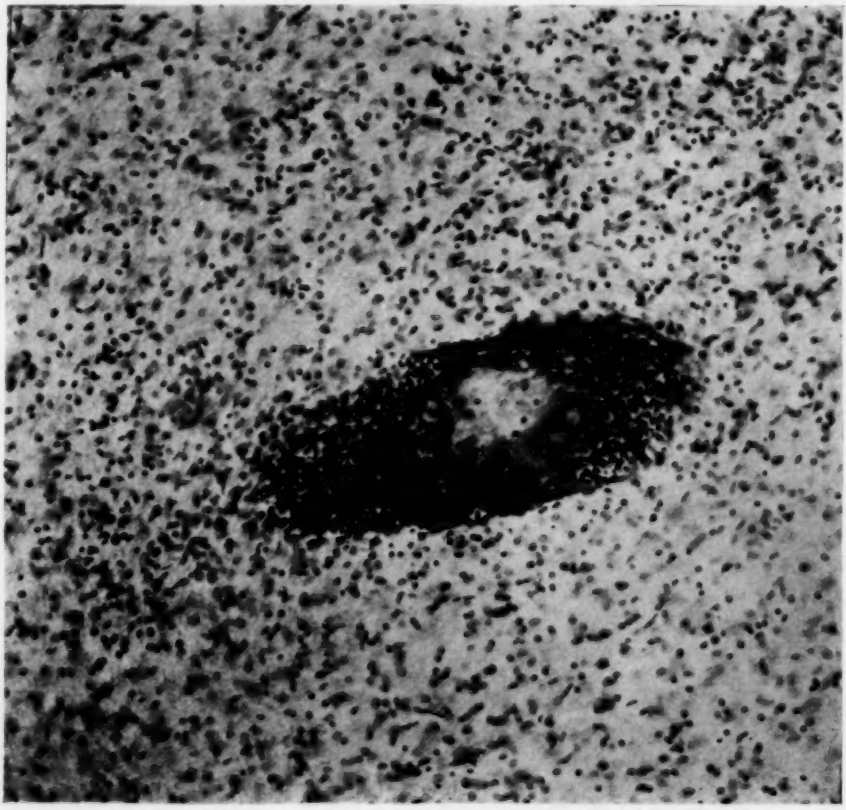

Fig. 1 (case 1).—Perivascular accumulation of round cells and polymorphonuclear leukocytes in globus pallidus; × 250.

and the cellular elements were numerous. They consisted mainly of round cells, polymorphonuclear leukocytes and large mononuclear cells.

The molecular layer of the cortex was very cellular, with marked vascularity and proliferation of new capillaries. In the deeper layers, there was a marked increase in the number of oligodendroglia nuclei, which at times were so numerous as to obscure the cyto-architecture. These cells arranged themselves about or in the ganglion cells. The latter showed acute degenerative changes, with swelling, chromatolysis, vacuolation of the cytoplasm and disappearance of the nuclei. Only rarely was a calcified ganglion cell noted.

The medulla, especially in the subcortical region, showed an increase in cellularity of the protoplasmic glia and to a less extent of the microglia. There were small perivascular and interstitial glia nodules.

The changes in the parietal lobe were similar in extent and amount to those in the frontal lobe.

The histologic changes in the occipital lobe were similar to those in the frontal lobe, but were decidedly less extensive.

Beneath the ependyma of the caudate nucleus there was a marked proliferation of glia nuclei and fibers. Small hemorrhages were found in the Virchow-Robin spaces and in the spaces of His. The blood vessels in the vicinity were surrounded by oval and round cells, many of which contained iron and fat. The acute degeneration of the ganglion cells previously described was also found in this region. Many of the vessels in other localities were surrounded by thick coats of small round cells and polymorphonuclear leukocytes. Small irregular glial rosettes, as well as small calcified bodies, were found in the interstitial tissue.

In the pons, the leptomeninges were thickened and cellular, as over the frontal lobe. Along the medial longitudinal fasciculus were large nodules measuring up to 2 mm. in diameter, which were composed of small oval and round cells filled with fat. Numerous dilated capillaries were seen coursing through these nodules. The vessels in the vicinity were cuffed by numerous fat-filled cells. There were no leukocytes present.

In the cerebellum, the changes in the meninges were similar to those described. The molecular zone was markedly vascular with capillary proliferation. The substantia nigra and the cornu ammonis showed no striking changes.

Case 2.—A colored girl, aged 3 years, the twin of the patient in case 1, entered the hospital nine months later with continuous convulsions. One year before, she had been paralyzed on the left side but had recovered in a few months. Since then she had had severe headaches on and off, but was apparently well until four hours before admission, when continuous convulsions developed.

The patient had had measles, whooping cough and chickenpox. She had been deaf and dumb since birth.

The child was well nourished and well developed. She was semicomatose, with continuous clonic convulsions involving the entire body and the face. There were râles in the bases of both lungs, posteriorly. Other physical findings were impossible to elicit because of the convulsions. The temperature was 99 F.; the pulse rate, 120 per minute, and the respiratory rate, 26 per minute.

The spinal fluid was under moderate pressure; it was clear, and gave a 4 plus reaction to the Pandy test; the cell count was 122 per cubic millimeter. A culture and the Wassermann reaction were negative.

The child died within a few hours after hospitalization.

The thymus weighed 16 Gm.; it was a light purple-gray and parenchymatous. The heart weighed 70 Gm.; the chambers were dilated, and the myocardium was pale and friable. Large patches of bronchopneumonia were found in both lower pulmonary lobes and in the upper lobe of the left lung. The spleen weighed 40 Gm.; the consistency was soft, and the pulp was purple-gray, with pinhead-sized follicles. The liver weighed 445 Gm.; it was pale and had indistinct markings.

The essential changes were in the brain. It weighed 1,115 Gm.; the leptomeninges were thin and moderately congested. The frontal lobes felt distinctly firmer than normal, as did the entire substance of the brain. The gross appearance simulated that of the brain in case 1.

Microscopic Changes in the Brain.—In the frontal lobe, the leptomeninges were thickened by large mononuclear cells and fibrocytes. The subarachnoid space was

widened and was filled with large round cells, many of which contained sudanophil substance. In the loosened subpial layer compound granular corpuscles were seen. The marginal zone of the cortex was vascular and cellular. In the deeper layers of the cortex, there was a marked increase of glia nuclei, especially oligodendroglia nuclei. Neuronophagia and satellitosis were so marked in places as to obscure the architecture. There were other areas in which the number of ganglion cells was diminished or there were none, with an increase of the glia fibrils and the formation of sclerotic plaques. In these areas, many of the ganglion cells were replaced by concrements staining deeply blue (with hematoxylin) and occasionally showing dendrite-like extensions. Many of these deposits contained perifocal accumulations of oligodendroglia nuclei. About and in the walls of the precapillaries and capillaries were small and large granular deposits of calcium. In some vessels, the

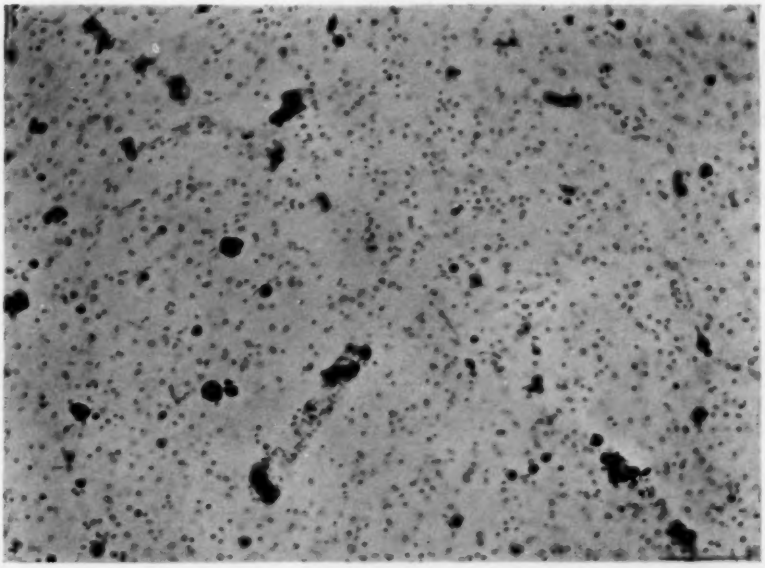

Fig. 2 (case 2).—Interstitial calcification and calcific deposits in the pericapillary spaces of the putamen; × 150.

aforementioned substance was in the form of homogeneous pale blue sheets or bands. Small cavities surrounded by glia fibrils and nuclei were found especially in deeper layers.

The medulla showed less marked changes. There was a slight diffuse increase of astrocytes, glia fibrils and Hortega cells. Some of the vessels were surrounded by fat-filled cells. Here, too, small cavities were found in the subcortical areas.

In the occipital lobe, the changes were similar to those in the frontal lobe, but were less marked, especially the number of deposits of calcium.

The changes in the parietal lobe were similar to those in the frontal and occipital lobes, but were more extensive. The concrements were more numerous, and in many instances they transformed the smaller arteries and capillaries into tubes of calcium.

Throughout the entire field of the putamen and globus pallidus were scattered dark blue bodies, varying in size from that of a red blood cell to that of a large

ganglion cell. They appeared singly or in clusters. Many of the concrements had a dark blue center and were surrounded by deep blue rings of varying intensity (hematoxylin stain). The smaller arteries, precapillaries and capillaries generally were surrounded by the blue granular or homogeneous deposit or their walls contained it. The extent of involvement varied from focal accumulations in the media or the spaces of Virchow-Robin and His to complete replacement of the walls. The intima was usually spared, although rarely the entire lumen was obliterated. As a rule, there seemed to be no active cellular response to the calcium. An occasional small cavity up to 1 mm. was found which showed perifocal gliosis. The ganglion cells evidenced acute degenerative changes.

In the caudate nucleus and the internal capsule, there were deposits of calcium but they were less extensive and were concentrated about the internal capsule.

In the pons, the leptomeninges were thickened and fibrotic. Scattered about were large mononuclear cells of the histiocytic type and a few small round cells. In the parenchyma were single, perivascular nodules which were composed of cells that had elongated or indented nuclei and cytoplasm containing fine chromatin granules. At the base of the fourth ventricle were recent perivascular extravasations of blood.

Moderate cellularity and vascularity were evident in the marginal zone of the cerebellum. Some of the vessels were surrounded by fat-filled cells. The Purkinje ganglion cells were well preserved, but an occasional cell and its branches were calcified.

The cornu ammonis, substantia nigra and cervical cord showed no noteworthy changes.

Case 3.—A colored girl, aged 6 years, was hospitalized three days following the death of her younger sister (case 2), with similar symptoms of convulsions. The mother stated that for the past year the child had shown signs of nervousness, vomiting and vague mental symptoms. The symptoms had been of sufficient intensity to warrant hospitalization one year before. The mother thought that in the past two weeks the child had had whooping cough. The cough had been continuous but nonproductive.

About one and one-half hours before admission, the child was playing, when suddenly she fell backward in an unconscious state and began having generalized convulsions. The attack lasted for twenty-five minutes, and the patient foamed at the mouth. She had been unconscious since then.

The mother was a septipara; five of the children had died as follows:

1. Died in 1925, aged 8 years; diagnosis, tuberculous pneumonia.
2. Died in 1925, aged 2 years; diagnosis, convulsive syndrome; autopsy records were not available but tuberculosis was excluded.
3. Died in 1930, aged 2 years and 9 months (case 1). } twins
4. Died in 1931, aged 3 years and 7 months (case 2). }
5. Died in 1931, aged 6 years (case 3).

The children were born at home; the births were apparently normal and at full term. The mother had had no miscarriages.

The patient sat up at 6 months, walked at 1 year and spoke words at 14 months.

The child was well nourished and semicomatose. There were continuous jerky, irregular, generalized, clonic twitchings of the entire body, but especially of the face, the neck and the upper extremities. At times the convulsions became more intense.

The temperature was 96 F.; the pulse rate was 90 per minute, and the respirations were shallow and jerky.

The eyeballs deviated from side to side in irregularly oscillating nystagmoid movements. The pupils were small, even and equal. The jaws were clenched. The reflexes were brisk, but difficult to elicit.

The spinal fluid was under increased pressure; the reaction to the Pandy test was 4 plus, and the cell count was 128 per cubic millimeter. The Wassermann reaction of the spinal fluid was negative.

The impression, in view of the previous cases in the same family, was of gliosis of the brain.

The child died within a few hours.

The thymus weighed 35 Gm., and was pale gray and parenchymatous. The heart weighed 95 Gm.; the myocardium was reddish brown and firm. The lungs were everywhere crepitant, moist and hyperemic. The spleen weighed 40 Gm.; the

Fig. 3 (case 3).—Calcification of a small artery in the putamen. Note that the involvement is mainly of the media and adventitia, the intima being practically free; × 250.

capsule was thickened, and the pulp was soft and purple-gray. The liver weighed 565 Gm.; the markings were distinct, and the parenchyma was pale.

The essential changes were in the brain. The leptomeninges over the convexity were thin, while there were slightly thickened, pale gray plaques over the base. The consistency of both cerebral hemispheres and, to a lesser extent, of the cerebellum was markedly increased. The appearance of the brain simulated that of the other two described.

The middle ears were free from abnormalities.

Microscopic Changes in the Brain.—In the frontal lobe, the leptomeninges were much thickened as a result of an increase in fibrous tissue, fibrocytes, large mononuclear cells and small round cells. In the sulci the subarachnoid spaces were

much widened and filled with similar cellular elements. Some of the histiocytic elements contained small fat droplets.

In the deeper layers of the cortex, the cyto-architecture was poorly preserved. There appeared to be focal areas of atrophy in which the number of ganglion cells was diminished or there were none, with an increase in the glia fibers. In these areas calcification of the ganglion cells was evident. (The microchemical reaction will be discussed later.) About many of these concrements were accumulations of oligodendroglia nuclei. In other places, the ganglion cells showed signs of acute degeneration. Surrounding some of the blood vessels were fat-filled cells.

The white matter showed a generalized increase of astrocytes, oligodendroglia and Hortega cells. Occasionally there were small cavities in the subcortical area.

In the occipital lobe, the leptomeninges were thickened, as over the frontal lobe. The cortical and medullary findings were also similar, but less marked.

Although the changes in the parietal lobe were similar to those in the frontal lobe, the calcification of the ganglion cells and the blood vessels was more extensive.

Deposits of calcium were found in the putamen and the globus pallidus. Scattered throughout were irregular glia nodules which were not related to vessels. In other places, small cavities were surrounded by glia fibrils. The walls of some of these cavities contained free or intracellular fat. About the vena terminalis beneath the ependyma were perivascular accumulations of glia nuclei, especially Hortega cells. Many of the latter contained a light brown pigment.

In the pons, the leptomeninges were much thickened by fibrillar connective tissue, histiocytes and large mononuclear cells. Some of the histiocytes contained small concretions of calcium. The vessels were surrounded by coats of small round cells. In the substance of the brain beneath the leptomeninges were small focal accumulations of round cells.

The marginal zone of the cerebellum was vascular with many branched capillaries.

The cornu ammonis and substantia nigra showed no noteworthy changes.

Levaditi preparations were negative for Spirochaeta pallida.

GENERAL REVIEW OF OBSERVATIONS

Clinical Findings.—There were many similarities in the three cases reported. The history of the child who died in 1925 at the age of 2 years resembled that of the patients in the cases reported, but the observations made at autopsy were not available except that tuberculosis was excluded. (An older child died the same year of tuberculous pneumonia.)

The cases were characterized by repeated attacks of symptoms referable to the central nervous system. The onset was insidious, with symptoms of slight headache, nervousness and vomiting, so that attention at first was not drawn to the brain. The actual attacks were more acute, with paralysis in the first case and extreme nervousness and vomiting in the first and third cases. The terminal syndrome was most severe, with semiconsciousness and convulsions.

The physical findings, when it was possible to elicit them, showed a hypertonic state with active reflexes, meningeal irritation in case 1 and nystagmus and trismus in case 3. The temperature was not characteristic, being slightly elevated in cases 1 and 2 and subnormal in case 3 (terminal state). The patient in case 2, in addition, had bronchopneumonia.

The laboratory findings were not constant. The spinal fluid was under slightly increased pressure; the cell count varied from 40 to 128 per cubic millimeter; the reaction to the Pandy test was positive in cases 2 and 3. The blood findings were not abnormal. The Wassermann reactions of the spinal fluids were negative.

Postmortem Observations on the Brain.—Macroscopically, the leptomeninges appeared only slightly congested, and at the base, as a rule, they were thickened and pale gray. The cerebral hemispheres in the three cases were distinctly smaller and firmer than normal. In case 1, the gyri of the frontal lobe were especially narrow.

In the other organs there were changes suggesting a moderately intense intoxication or infection. In case 2 there was frank bronchopneumonia of long duration.

Microscopically, case 1 presented changes somewhat different from those in cases 2 and 3, although both groups were characterized by older and more recent lesions.

In case 1, the intensity of the pathologic changes varied in the different regions of the brain in the following order: pons, central ganglion (caudate nucleus, globus pallidus and putamen), cortexes of the frontal, parietal and occipital lobes and medullary portions of these lobes. The recent changes were characterized by acute degeneration of the ganglion cells, rarefaction and hemorrhages; proliferation of the capillaries and of the cellular glia, both perivascular and in rosettes, and perivascular accumulations of lymphocytes and polymorphonuclear leukocytes. The more chronic alterations were the proliferation of the glial fibrils, the fibrous tissue proliferation of the leptomeninges and finally the nodules composed of fat-filled cells, proliferated glia and capillaries.

The changes in cases 2 and 3 were somewhat similar. The most intense involvement was in the putamen and globus pallidus, and then in the cortexes of the parietal lobe, frontal lobe and occipital lobe, the medullary portions of these lobes, the pons, the caudate nucleus and the internal capsule. The acute degeneration of the ganglion cells and the rarefaction were decidedly less marked than in case 1, and hemorrhages were found only in case 2. Proliferation of the cellular glia was extensive, but lymphocytes were rare and granulocytes absent.

Irregular glia nodules [13] were found in the putamen and globus pallidus in case 3. These advanced changes superseded the acute ones. Decrease to absence of ganglion cells in the focal areas, with scar formation, in the cortex and calcification of ganglion cells, as well as small arteries, precapillaries and capillaries, predominated. Small cavities were found in the globus pallidus, putamen, cortex and subcortical zone of the medulla. Many of the cavities showed a perifocal increase of glia fibrils, and their peripheries contained free or fat-filled cells. The meninges, especially in case 3, presented fibrosis, which was most marked at the base.

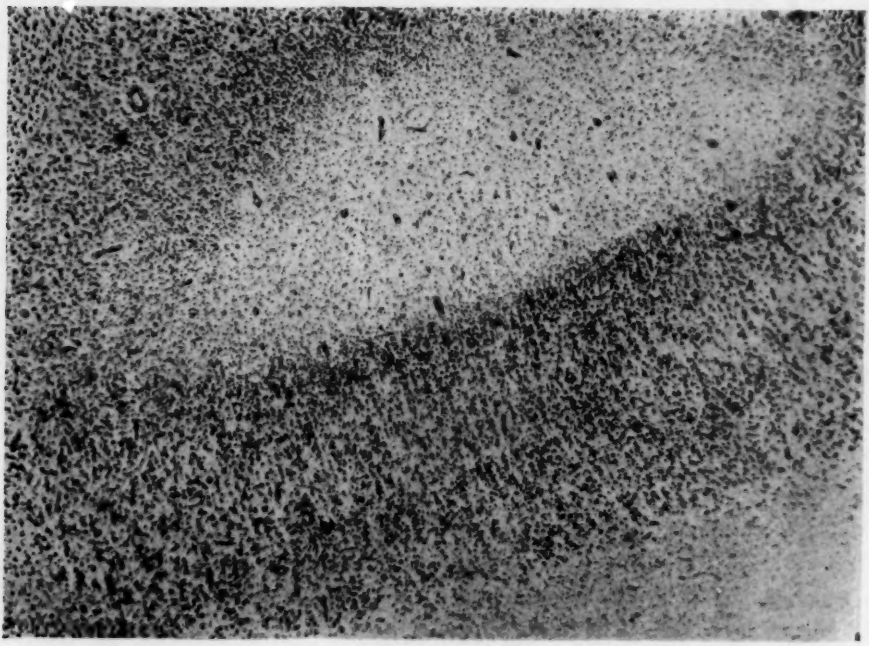

Fig. 4 (case 3).—A sclerotic plaque in the cortex of the parietal lobe. Note the calcified ganglion cells about the sclerotic area. Toluidine blue stain; × 50.

MICROCHEMICAL REACTIONS OF CONCRETIONS IN THE BRAIN

The concretions free in the parenchyma and in the ganglion cells stained deeply with hematoxylin or hemalum. In some instances concentric rings were noted about a dark blue center. In the vessels the staining reactions varied from a diffuse, homogeneous, pale blue to a coarsely to finely granular dark blue. With toluidine blue, the concrements usually stained deep blue, but at times were not stained by this method. With sudan III, the reaction was negative.

13. The glia nodules were distinctly different from the focal germinal areas commonly found in the brains of small children.

Calcium Reactions.—With the addition of acid, small gas bubbles formed underneath the cover glass.

With the method of Roehl, the concretions stained intense violet.

An interesting observation was that in the stained preparations (with hematoxylin and eosin), the application of a 5 per cent solution of nitric acid resulted in a dissolution and decolorization of the majority of the concrements, with the formation of small gas bubbles, but here and there some of the concretions did not become decalcified or decolorized. Furthermore, after being washed thoroughly with water and stained with Ehrlich's or Böhmer's hematoxylin, most of the decalcified deposits stained blue. This was also the case with the vessels.

Iron Reactions.—Perl's reaction was positive in the walls of the calcified vessels and with the concrements in the region of the central ganglion, but only occasionally positive in the calcified ganglion cells of the cortex.

Optic Reactions of the Concretions of Calcium.—Dark-field and polariscopic methods showed no refraction.

After decalcification the bodies were refractile and glistening.

INTERPRETATION OF THE PATHOLOGIC CHANGES

From a microscopic standpoint, the determination of the age of a lesion in the brain is extremely difficult. The inflammatory changes in this organ, for instance, are in no way parallel to the duration of the disease (Spatz,[14] Jacob,[15] Spielmeyer [12] and others). Disease processes may disappear quickly or may remain for years. Thus, relatively acute changes were found in the brain by Jacob after four years, by von Economo [16] and Goldstein [17] after two years, by Spielmeyer after one year and by Spatz after four months. In many instances, one must resort to the history for an accurate determination of the age of a lesion (Wohlwill [18]). There are, however, some gross and microscopic features which suggest chronicity.

In all three cases cited, the gross appearance of the brain spoke in favor of a long-standing process, i. e., the firmness of the cerebral hemispheres, the atrophy of the convolutions and the absence of marked hyperemia.

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14. Spatz, H.: Ztschr. f. d. ges. Neurol. u. Psychiat. **77**:261, 1922; Encephalitis, in Handbuch der Geisteskrankheiten, Berlin, Julius Springer, 1930, vol. 11, pt. 7.

15. Jacob, Alfons: Normale und pathologische Anatomie und Histologie des Grosshirns, Vienna, Franz Deuticke, 1927.

16. von Economo, Constantin: Die Encephalitis lethargica, ihre Nachkrankheiten und ihre Behandlung, Berlin, Urban & Schwarzenberg, 1929.

17. Goldstein, K.: Ztschr. f. d. ges. Neurol. u. Psychiat. **76**:627, 1922.

18. Wohlwill, F.: Klin. Wchnschr. **5**:805, 1926.

Microscopically, in the first case some lesions were much older than others. Thus, the fibrous thickening of the meninges and the nodules of fat-filled cells in the pons were older than the perivascular accumulations of lymphocytes and polymorphonuclear leukocytes in the globus pallidus and the putamen. The granulocytic and round cell infiltrations of the fibrous meninges suggested that an acute process had been superimposed on a chronic healed one, for there was no intermediary stage of proliferation and plasma cells, histiocytes and fibrocytes. Many of the chronic changes in the brain proper were undoubtedly obscured by the acute process.

The changes in cases 2 and 3 similarly suggested the superimposition of an acute process on a chronic one. The small cavity formation and the atrophic, sclerotic plaques in the cortex were compatible with a long-standing process, in many instances arrested. The calcification also substantiated chronicity, although Jacob believes that it may occur in acute lesions. On the other hand, the acute degeneration of the ganglion cells, the perivascular accumulation of glia nuclei and the interstitial nodules resembled an acute process, as was indeed brought out by the history.

It appears, then, that in the three brains there was an underlying chronic process on which was superimposed an exudative lesion in the first case and a degenerative lesion in the second and third cases.

What is the pathogenesis of the primary chronic process, and what is the nature of the complications?

PATHOGENESIS OF THE PRIMARY PROCESS

In 1867, Virchow [19] described small yellow nodules in the medulla of the cerebral hemispheres of new-born infants which microscopically were composed of groups of fat-laden cells. Because some of the cells were swollen and others proliferated, simulating the cellular reaction in inflammation, Virchow believed that the condition was infectious, designating it as "interstitial encephalitis of the newborn." Etiologically, he considered syphilis and the acute exanthems, especially smallpox. In 1871, Jastrowitz [20] reported that the appearance of fat-laden cells in the medullary portion of the cerebrum was a normal physiologic process up to the eighth month and was related to the formation of the myelin sheath. On the strength of this work, Virchow published a second paper in 1883 in which he conceded that the condition which he had described might not be infectious, but at any rate was of a progressive character. The matter lay dormant until recently (1920),

19. Virchow, R.: Virchows Arch. f. path. Anat. **38**:129, 1867; Berl. klin. Wchnschr. **19**:706, 1883.

20. Jastrowitz, M.: Arch. f. Psychiat. **3**:162, 1871.

when the entire subject was again opened, and a middle stand was taken by Ceelen,[21] Wohlwill[18] and others, in that they believed that the fat in question was either anabolic or catabolic, the latter usually resulting from infection (von Limbeck,[22] Ceelen,[21] Schmincke[23]). Shortly afterward, Schwartz,[24] Siegmund[25] and Gross[26] (1922) took the stand that the presence of fat in the brain was always pathologic, and they agreed with Parrot[27] (1868) that it was the result of trauma sustained at birth.

Schwartz[24] stated in his excellent paper that even in so-called normal deliveries, the difference between the intra-uterine pressure (after rupture of the bag of waters) and the atmospheric pressure is so great that destructive changes affecting the head (especially if lowest in the pelvis) are inevitable. The decreased pressure in the region of the brain at times causes the blood to rush there with sufficient force to rupture blood vessels. Of equal importance is the pressure exerted on the substance of the brain, which almost always shows the effects of such insults.

The same author, in studying the brains of animals (calves, rabbits, dogs, cats, hogs and chickens), found that without the stresses and strains of labor the brains of the new-born do not show fat in the nerve substance, the interstitial tissue and the ganglion cells. One may find a few fat-laden cells along the blood vessels in such cases. After a so-called normal delivery, only a small percentage of animals and human beings have normal brains, as described.

In the majority of the new-born there are some changes in the brain following labor, a fact not difficult to conceive considering the soft skull and watery brain. According to Schwartz,[24] the milder types of lesions consist in (excluding hemorrhages) a loosening of the substance of the brain, and, if more extensive, a vacuolation of this substance. When loosening occurs, the lesion remains stationary for from three to four days. About the fifth or sixth day, necrosis sets in, with destruction of the ganglion cells, axis cylinders, glia and other elements. By the sixth or eighth day, fat-laden cells appear, and organization begins. This organization may take from months to years; the fat is removed, the glia proliferates, and a small scar results which may be difficult to find. A similar process takes place in the reparation of vacuolation

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21. Ceelen, W.: Virchows Arch. f. path. Anat. **227**:152, 1920.
22. von Limbeck, R.: Ztschr. f. Heilk. **7**:87, 1886.
23. Schmincke, A.: Ztschr. f. d. ges. Neurol. u. Psychiat. **60**:290, 1920.
24. Schwartz, P.: Ergebn. d. inn. Med. u. Kinderh. **31**:165, 1927.
25. Siegmund, H.: Klin. Wchnschr. **1**:2274, 1922; München. med. Wchnschr. **70**:137, 1923.
26. Gross, W.: Centralbl. f. allg. Path. u. path. Anat. **33**:225, 1922.
27. Parrot, J.: Arch. de physiol. norm. et path. **1**:622, 1868.

of the substance of the brain. Small vacuoles may be replaced by scar formation, but larger ones remain as cavities surrounded by glia fibrils. In the latter, deposits of calcium and of iron may be found. Schwartz designates the stage in which accumulations of fat are seen as "presclerotic," and the stage of gliosis and scar formation as "sclerotic."

These lesions may occur in any portion of the brain. Most commonly, however, they are found in the frontal and occipital medullary portions, in the part drained by the vena terminalis and vena lateralis and in the basal ganglions, cortex and medulla oblongata.

The late stages may be summarized as follows: (1) decrease of cell masses in the areas of scarring; (2) hardening of the brain substance as a result of the production of glia fibrils; (3) disturbance of the architecture of the cells through degeneration, with disappearance and calcification of the ganglion cells and accumulations of granulations between organizing glia cells; (4) disturbance of the architecture of the medulla as a result of degeneration of nerve fibers and replacement by scar tissue; (5) resulting small cavities consequent to vacuolation of nerve substance, and (6) small, especially firm scars resulting from small loosened areas.

Although, in the main, the work of Schwartz has been accepted (Ylppö,[28] Wohlwill,[18] Seitz,[29] Mayer,[30] Siegmund,[25] von Kruska[31]), there are important features which are held open to question. Wohlwill, for instance, accepts the more extensive lesions following trauma sustained at birth, which are manifested clinically by paralysis, nystagmus, idiocy and epilepsy, but takes a neutral to negative stand concerning the milder types of lesions, with few or no clinical symptoms, and the microscopic appearance of "presclerosis" or "sclerosis." This author believes that clinical manifestations offer the better basis for judgment, a point which must be conceded. But what is difficult to understand is why the milder involvements are so strenuously attacked, if such extensive lesions as microgyria, porencephaly, lobar atrophy and sclerosis are accepted as traumatic complications sustained at birth and are compatible with adult life. It appears more logical to assume that the milder lesions should be more common than the severe ones, and it is perhaps because of difficulty in recognition or because of overshadowing by some complication that they are not found.

In the three cases described, the underlying chronic lesions presumably had their origin in trauma at birth. In the first case, the

28. Ylppö, A.: Ztschr. f. Kinderh. **20**:212, 1919.

29. Seitz, L.: Arch. f. Gynäk. **82**:528, 1907.

30. Mayer, A.: Zentralbl. f. Gynäk. **39**:795, 1915.

31. von Kruska, B. G. T.: Ueber Geburtsläsionen der Gehirnsubstanz, speziell die ischämischen Nekrosen und ihre Folgezustände, Inaug. Dissert., Halle, 1915.

presclerotic stage was seen, but sclerotic manifestations were probably obscured by the more acute process. In the second and third cases, the presclerotic, but more markedly the sclerotic, stages were evident. That these children were especially exposed to injuries at birth can be judged by the following facts: The children were colored and it is a long-established fact that colored women most frequently have contracted rachitic pelves. The patients in cases 2 and 3 were twins, which speaks for increased insults at birth (Wohlwill [18]). Three of seven children (and probably a fourth) presented rather similar clinical and pathologic changes, with nervous symptoms dating back from four months to one year. (As will be discussed later, the symptoms were probably of longer duration.)

PATHOGENESIS OF SUPERIMPOSED EXUDATIVE LESION IN CASE 1

One of the most difficult problems in neuropathology is the microscopic differentiation of inflammatory from noninflammatory conditions. Indeed, the reactions at times are so similar that the distinction from a microscopic standpoint is only nominal, being dependent on bacterioscopic and cultural findings and animal inoculations. Thus one distinguishes an "inflammatory reaction" (Spatz [14]), an "encephalitic symptom complex" (Spielmeyer [12]) or "encephalopathy" (Aschoff [32]) from an inflammatory disease" (Spatz [14]) or "true encephalitis" (Spielmeyer,[12] Aschoff [32]) more by the bacterioscopic studies than by histologic characteristics. Unfortunately, even the bacterioscopic findings and the animal inoculations may be negative in obvious inflammatory diseases.

In the first group of cases, the pathologic changes underlying the "inflammatory reaction" may be found, such as hemorrhages and areas of softening. In the second group of cases, the predominance of cellular infiltration, especially granulocytes, and the relatively small number of granule cells may aid in the diagnosis. In both groups, however, the basic reactions are similar, i. e., a cellular infiltration (leukocytes, lymphocytes, mast cells, plasma cells and macrophages), in addition to a reaction of the glia.

The difficulty in deciding the etiology of the infiltrating reaction in case 1 is at once apparent, especially since no animal inoculations were carried out (cultures of the spinal fluid were negative). Yet there were certain paramount features which spoke in favor of an "inflammatory disease." In the regions in which the reparative lesions were found (pons), the granule cells were numerous both in the direct vicinity and about the more remote vessels. Granulocytes were not found in this region, and lymphocytes were rare. In distant parts (putamen, globus pallidus) devoid of presclerotic areas, the perivascular infiltra-

32. Aschoff, L.: Beitr. z. path. Anat. u. z. allg. Path. **71**:19, 1922.

tions consisted of many lymphocytes and polymorphonuclear leukocytes, but few granule cells. The leukocytic infiltration of the meninges was also suggestive of an inflammation.

In many respects, the foregoing histologic picture simulates epidemic encephalitis. Early in this condition (from the second to the third day) perivascular and meningeal leukocytes appear (von Economo,[16] Spatz,[14] Bassoe and Hassin [33]) among the other infiltrative elements. The irregular glia nodules ("fleckförmig") not associated with vessels were found in case 1. The location of the process, however, was dissimilar. Whereas in epidemic encephalitis the nucleus caudatus and putamen are usually spared (von Economo,[16] Spatz,[14] Ernst), in the case described, the putamen and globus pallidus were the sites of predilection.

The other types of true encephalitis listed by Wohlwill [18] as occurring in children may be excluded as follows: encephalitis in association with meningitis, because the changes in the brain were older and more severe than the changes in the meninges, although clinically meningeal irritation was evident; encephalitis associated with acute infectious diseases, because of the negative history and postmortem observations; purulent encephalitis, because of the absence of suppuration; polioencephalitis haemorrhagica superior of Wernicke and purpura of the brain of other etiology, because of the absence of extensive ring hemorrhages and vascular proliferation in the midbrain; encephalitis degenerativa or encephalitis congenita, already discussed. The latter three types of encephalitis should be considered as pseudo-encephalitis ("inflamatory reaction," Spatz [14]).

There remains to be explained, then, the acute manifestations in case 1, a superimposed inflammatory disease secondary to a cryptogenic focus not disclosed by the history or by the postmortem observations or an atypical form of epidemic encephalitis. That the entire process is one of epidemic encephalitis is unlikely, because of the clinical history and the absence of scarring and a decrease in the size of the black zone, the substantia nigra (Goldstein,[17] Jacob,[15] Spatz,[14] Wilckens [7]).

PATHOGENESIS OF THE DEGENERATIVE PROCESS OR INFLAMMATORY REACTION IN CASES 2 AND 3

The absence of granulocytes does not necessarily exclude true encephalitis, but the large degenerative zones and the presence of many granule cells laden with fat and pigment suggest an inflammatory reaction rather than disease. This process, although still active, suggested chronicity, because of the cavity formation, the atrophic areas in the cortex and the calcification. In many places arrested lesions

33. Bassoe, P., and Hassin, G. B.: Arch. Neurol. & Psychiat. **2**:24, 1919.

were evident, as cortical scars or deposits of calcium without an active glial response. Yet the presence in other localities of marked acute degeneration of the ganglion cells with glial proliferation, perivascular and in nodules, suggested a more recent toxic agent. This was borne out by the clinical history, in that the children, although having clinical manifestations related to the central nervous system for one year, appeared much improved, and then were suddenly taken ill and shortly afterward died with symptoms of acute cerebral disturbance.

The cause of the exacerbation in the second case may be related to the extensive bronchopneumonia, while that in the patient in the third case, who lived in the same house, might be explained similarly, except that in the latter only an infection of the upper respiratory tract developed, as was manifested clinically by cough. The mother interpreted the cough as of the whooping character, but this could not be substantiated in the hospital or anatomically. This possibility was not entirely ruled out, as the acute degeneration of the ganglion cells in the cortex, especially in the parietal lobe, might well be explained by a whooping cough encephalitis (Spielmeyer [12]), but the absence of the linear arrangement of the cells in the cornu ammonis as well as ring hemorrhages (in the eclamptic form) suggested another etiology.

It is more likely that the bronchopneumonia on the one hand and the infection of the upper respiratory tract on the other were responsible for the inflammatory reactions being superimposed on an already damaged brain.

RELATIONSHIP OF TRAUMA SUSTAINED AT BIRTH TO ENCEPHALITIS

Experimentally, the injection of bacteria into the carotid artery or the aorta rarely produces encephalitis, and then only in brains that have been injured in one way or another (Lamy [8]). The injection of small emboli with the bacteria produces lesions in the brain with greater frequency (Lhermitte and Schaeffer [34]). The latter phenomenon is explained by the fact that the embolus injures the substance of the brain so that the organisms come in direct contact with the parenchyma. Thus, the injection of bacteria directly into the substance of the brain invariably leads to encephalitis (Homén [35]).

Applied to man, isolation of bacteria from cerebral vessels in cases of streptococcic, staphylococcic and pneumococcic septicemia is accomplished in 75 per cent of cases (E. Frankel [8]); yet encephalitis in these instances is rare. In vegetative or verrucous endocarditis, the incidence of encephalitis is much higher (Spatz,[14] Diamond [36]), partly because

34. Lhermitte, J., and Schaeffer, H.: Semaine méd. **30**:25, 1910.
35. Homén, E. A.: Arb. a. d. path. Inst. zu Helsingfors **2**:1, 1919.
36. Diamond, I. B.: Arch. Neurol. & Psychiat. **27**:1175, 1932.

of the associated emboli. Also, it is common knowledge that encephalitis may follow injuries to the head, in which a mild infection of the upper respiratory tract may initiate the disease. Indeed Aschoff has repeatedly demonstrated such cases at his pathologic conferences.

In other parts of the body, the relationship between injury and inflammation is a long-established fact (osteomyelitis, tuberculosis of the bone and the lungs). Yet little stress is placed on the association of such widely prevalent and at times extensive lesions as traumatic injuries sustained at birth with inflammatory or toxic conditions of the brain and spinal cord. There can be no doubt that the brain, thus injured, is a focus of lowered resistance and a prey for bacteria and toxins.

The first case reported demonstrated an inflammatory process, while the second and third cases showed toxic ones, superimposed on traumatic lesions sustained at birth. The attacks, as described clinically (transient paralysis, vomiting, mental disturbances), demonstrate the susceptibility of the brains of such persons to infections and toxic irritants.

One should inquire more thoroughly into the encephalitis of unknown origin, the atypical and sporadic types of epidemic encephalitis with clinical signs of hemiplegia or diplegia and, finally, the toxic forms of encephalitis in which the etiology is obscure or follows a pyogenic focus. It is likely that in many of the foregoing instances the underlying pathogenesis has its origin in a trauma sustained at birth, and that the toxic or inflammatory irritants, obvious or obscure, virulent or avirulent, find a devitalized, susceptible ground for their activities. It must be borne in mind that the more acute process may easily overshadow the chronic one.

PATHOGENESIS OF CALCIFICATION IN THE BRAIN IN RELATION TO TRAUMA SUSTAINED AT BIRTH

Calcific changes in the brains of children are rare (Jores, Jacob [15]). They have been described as associated with traumatic lesions sustained at birth, including so-called Virchow's interstitial encephalitis (Parrot,[27] Schmincke,[23] Schwartz [24]); with carbon monoxide poisoning (Herzog,[37] Wohlwill [18]); with epidemic encephalitis (Dürck,[38] Siegmund [25]); with tetany (Schnabel,[39] Ostertag [40]); with mongolian idiocy (Jacob,[15] Ostertag [40]), and with conditions of unknown etiology

37. Herzog, G.: München. med. Wchnschr. **22**:558, 1920.

38. Dürck, H.: Ztschr. f. d. ges. Neurol. u. Psychiat. **72**:175, 1921; Verhandl. d. deutsch. path. Gesellsch. **18**:88, 1921.

39. Schnabel, H.: Centralbl. f. allg. Path. u. path. Anat. **33**:226, 1922.

40. Ostertag, B.: Virchows Arch. f. path. Anat. **275**:828, 1930.

(Sauer [41]). Many of the cases in which calcification is reported, however, must be considered with skepticism, because there appears in brains at all ages as a supposed incidental finding a noncalcium-containing substance which simulates calcium in morphology and in location.

In the older literature, these deposits were considered as pathognomonic of chorea (Elischer,[42] Flechsig [43]), and from time to time they are rediscovered in other diseases. More recently these bodies have been found in 72 per cent of the brains of patients dying of various diseases and at all ages (Kodama,[44] Ostertag [40]).

Similar to the concretions of calcium, this pseudocalcium (Spatz,[14] Ostertag [40]) appears in the brain in three forms: (*a*) free in the tissue, as small granules which may become confluent, assuming the shape of a mulberry; (*b*) in the same form, but about the walls of the capillaries, sometimes replacing the capillary wall and obliterating the lumen; (*c*) in the walls of arteries, appearing as homogeneous or granular masses.

In regard to location, calcium and pseudocalcium are found most frequently in the globus pallidus and the putamen. In the cases reported, deposits of calcium were frequently seen replacing ganglion cells and in the walls of the vessels of the cortex, a property not described as common to pseudocalcium.

Calcium and pseudocalcium both have an affinity for basic dyes. It is the deep blue staining with hematoxylin that confuses the two. Calcium gives positive reactions with the Roehl and Kossa methods for calcium, whereas pseudocalcium does not. The application of dilute nitric acid yields gas bubbles with the concrements of calcium only. Another point of differentiation, as I have shown, is the application of dilute acid to sections stained with hematoxylin. The calcium becomes decolorized and gas bubbles form, whereas the pseudocalcium is not decolorized and no gas is produced.

Mallory [45] and, independently, Hansemann [46] were the first to show that there was a close relationship between pseudocalcium and calcium. By decalcifying the vessels of the brain, they found that there remained a refractile substance which had a marked affinity for hematoxylin. This fact was also noted in the cases reported, but included interstitial deposits of calcium and calcified ganglion cells. Mallory concluded that the ground substance was a colloid material and the basis for all calcification of the vessels of the brain.

41. Sauer, W.: Ztschr. f. Kinderh. **46**:457, 1928.
42. Elischer, J.: Virchows Arch. f. path. Anat. **63**:104, 1875.
43. Flechsig, P.: Verhandl. d. Cong. f. inn. Med. **7**:452, 1888.
44. Kodama, F., quoted by Ostertag.[40]
45. Mallory, F. B.: J. Path. & Bact. **3**:110, 1894-1896.
46. Hansemann, H.: Verhandl. d. deutsch. path. Gesellsch. **2**:399, 1898-1899.

The true nature of this colloid, as of colloids in general, is not known. It is insoluble in alcohol, ether and chloroform, and reactions for glycogen and amyloid are negative (Ostertag [40]). The addition of water or a weak alkaline solution causes this substance to swell and lose its glistening and refractile properties. Perl's reaction for iron is rather constant (Perusini [47]), especially if concentric rings are present (Ostertag [40]). However, this property is dependent on the presence of iron in the vicinity (Spatz [14]). In children, the colloid gives a positive reaction only if iron has appeared in the brain (Spatz [14]). Thus the colloid in the region of the central ganglions in cases 2 and 3 gave a positive reaction for iron (Perl's) because of the abundance of iron there, but that in the region of the cortex gave such a reaction only rarely, because of the paucity of iron there. The vessels, wherever calcified, gave this reaction.

That the blue staining of the colloid with hematoxylin might be explained as a result of the iron content (Wells [48]) must be borne in mind. In such instances, however, the hematoxylin stains lightly. As reported, the colloid stained deeply with hematoxylin, and iron was rarely demonstrated in the deposits in the cortical ganglion cells, although the strong affinity for the basic dyes remained.

The pathogenesis of this colloid substance is even less clearly understood. It is believed to occur when there is an alteration of the tissue metabolism and when the tissue fluids become stagnant and are precipitated. Thus it is seen at the junction of healthy and diseased tissues, as in cases of tumors, dementia paralytica, amaurotic family idiocy and other conditions. Similarly, Ostertag [40] explains the occurrence of the colloid bodies at the junction of the globus pallidus with the internal capsule and putamen as the result of a change in the type of metabolism. Why there should be such a change at this point only has not been clearly ascertained.

When one considers the positive factors concerning the deposit of calcium and compares them with the salient features of traumatic lesions sustained at birth, a more likely explanation is evident. First, the occurrence of the deposit at the junction of diseased or degenerated and healthy tissue corresponds closely to the site most commonly affected in injuries sustained at birth, namely, the region of the internal capsule. Second, the high incidence of colloid bodies reported by Kodama [44] and Ostertag [40] (72 per cent) corresponds to the high incidence of traumatic lesions sustained at birth.

What possibly takes place is that with the destruction of the tissue of the brain following insults at birth, much colloid substance is liberated. The latter remains locally or is transported by the tissue fluids

47. Perusini, G.: Folia neuro-biol. **6**:465, 1912.
48. Wells, H. G.: Arteriosclerosis, to be published.

or cellular elements to the perivascular spaces (the spaces of Virchow-Robin and of His). Because of the great affinity of elastic fibers for colloids (also mucin and calcium, Wells [48]), much of the colloid substance becomes deposited between the elastic fibers of the arteries. The veins having less elastic tissue are less frequently affected. In the perivascular spaces about the capillaries a stagnation occurs. The fate of the stagnant colloid is similar to the aging of colloid in general. This is characterized by a tendency to dehydration, a decrease in the degree of dispersion of the particles and the formation of larger particles which are less stable (Wells [48]). The homogeneous and granular deposits, as described in the text, may be explained by the latter mechanism. That such aging may come about in a relatively short time is readily seen by the changes occurring in the placenta, which becomes typically senile in nine months (Warthin,[49] Wells [48]).

It is with this stagnant, degenerating colloid as a basis that calcification sets in. According to the available evidence, calcium salts exist in the body fluids in three forms: in combination with proteins, in an ill-defined form which depends on parathormone (Greenwald [50]) and as simple inorganic ions in solution (Barr [51]). It is generally agreed that the amount of calcium dissolved in the serum is greater than can be held in solution by similar concentrations of phosphorus and carbonate (Hastings, Murray and Sendroy,[52] Holt, LaMer and Chown [53]). Whether or not a supersaturation of calcium takes place in the serum is not definitely proved, but that the equilibrium of the solution can easily be disturbed and calcium thrown out of solution is widely accepted (Kleinmann,[54] Barr [51]). Such a disturbance may be local, where it depends on a chemical alteration in the tissue. The nature of this disturbance has been best described by Kleinmann,[54] who demonstrated an alkalinity in devitalized tissue. In the presence of alkalinity, the tertiary calcium phosphate is precipitated in crystalline form. The latter in turn draws the calcium and carbonate from solution in the form of a mixed precipitate of calcium phosphate and calcium carbonate. Although this theory is the most plausible, it is still open to question, as it is based on supersaturation (Barr [51]). That alkalinity plays a determining rôle is evident in the fact that calcium metastases are found

49. Warthin, A. S.: Old Age: The Major Involution, New York, Paul B. Hoeber, Inc., 1929.

50. Greenwald, I.: J. Biol. Chem. **117**:1, 1926.

51. Barr, D. P.: Physiol. Rev. **12**:593, 1932.

52. Hastings, A. B.; Murray, C. D., and Sendroy, J., Jr.: J. Biol. Chem. **71**:723, 1927.

53. Holt, L. E.; LaMer, V. K., and Chown, H. B.: J. Biol. Chem. **64**:509, 1925.

54. Kleinmann, H.: Biochem. Ztschr. **196**:98, 1928.

only where acid is secreted or excreted in the tissues, signifying an alkalinity in that place (Askanazy,[55] Hofmeister [56]).

In summary, the pathogenesis of the calcification as seen in the cases reported was presumably dependent on the destruction of tissue resulting from injuries sustained at birth. There followed a liberation of colloid materials, which either remained locally or were carried to the perivascular spaces. Of the latter, part was carried away by the blood stream, part was attracted by elastic fibers of the arteries, and part remained stagnant in the pericapillary spaces. Owing to the stagnation, this colloid aged rapidly. Some of the colloid fell out of solution and became granular. As a result of the alkalinity of this devitalized substance, the tertiary calcium phosphate was precipitated. The latter caused the calcium and carbonate to be thrown out of solution in the form of calcium phosphate and calcium carbonate.

COMMENT

The microscopic diagnosis of injuries of mild character sustained at birth is subject to much error, especially if these injuries are observed late in childhood. One of Wohlwill's [18] chief criticisms of Schwartz' [24] work was that he found accumulations of fat-filled cells ("presclerotic stage" of Schwartz) in infants dying of grip. It is true that the early and late stages of inflammatory lesions of the brain may simulate foci due to trauma at birth. Also, sclerotic plaques and the formation of small cavities are common to both (Schwartz [24]). One may then reason that the chronic lesion described was the result of old encephalitis. Referring, then, to the history as suggested by Wohlwill,[18] it will be noted that the onset of the cerebral manifestations was insidious, with nervousness, vomiting and headaches which were so slight at first that pathologic changes in the brain were not considered. Such an onset in children would speak against encephalitis, whereas the acute attacks were typical of it. True, the time element of the symptoms does not go back to early infancy, but experience with histories from the class of colored patients coming to the Cook County Hospital has taught that such histories, at best, are inaccurate. In the first case, for instance, the child had been in the hospital four months before the second admission, and unquestionably had been ailing for some time to warrant the first hospitalization. Furthermore, many injuries sustained at birth present no clinical manifestations until late in life.

The macroscopic appearances of the brains described were singular and yet similar, suggesting a long-standing common process. Schmincke [23] described firm, grayish-white brains in a 9 month old

55. Askanazy, M.: Beiträge zur Knochenpathologie, Festschrift für Jaffé. Braunschweig, 1901.

56. Hofmeister, F.: Ergebn. d. Physiol. **10**:429, 1910.

infant and in a 1½ year old child. This author diagnosed the cases as Virchow's interstitial encephalitis, but, as has already been stated, they belong to the group of traumatic lesions sustained at birth. The time required for a brain to become firm, with shrinking of the gyri, is therefore not definite.

Another point difficult to explain is the assertion that in all cases both an older lesion and a recent one existed. As a rule, this assertion is not possible, and in cases 2 and 3, it might be doubted. But here again the history is suggestive of an acute attack initiated by bronchopneumonia, which was older than the duration of the encephalitic symptoms. In case 1, the leukocytic infiltration, especially of the meninges, where granulocytes and lymphocytes were present among fibrous connective tissues without the intermediary stage of plasma cells, histiocytes and fibrocytes, is a reliable indication of a superimposed acute infectious process.

SUMMARY

It has been suggested that in many cases of so-called idiopathic and atypical types of encephalitis in children the underlying cause may be the injuries sustained at birth. With the brain in a state of lowered resistance, cryptogenic or obvious infections may initiate encephalitis.

The clinical history in such cases may indicate a difficult or prolonged labor, although the morbidity in so-called normal labors is sufficient. The children may have signs referable to the central nervous system from birth, or these signs may be absent or so slight as to be overlooked. Repeated attacks of encephalitis should probably be considered pathognomonic, more especially if associated with paralysis. The temperature, spinal fluid findings and number of leukocytes in the blood depend on the severity of the superimposed infection.

The prognosis is not necessarily fatal and is dependent on the severity of the underlying injury and the virulence of the invading organism or toxin. Some of the cases in which the patient recovered described by Brain, Hunter and Turnbull,[1] Stooss[2] and Grinker and Stone[11] might fall in this group.

The macroscopic appearance of the brain may be normal if the injuries were slight, or may be altered by recent infection. In the more pronounced cases, small yellow nodules, grayish-white plaques or the formation of minute cysts may be seen. In severe injuries, the brain may be focally or diffusely firm, with shrunken gyri, most commonly of the frontal and occipital lobes. The most extensive lesions are hemorrhages, porencephaly, atrophy of the entire hemispheres or sclerosis of the hemispheres. The meninges may or may not be thickened; the falx cerebri and the tentorium cerebelli may show evidences of old rents or hemorrhages.

Microscopically, the presclerotic or the sclerotic foci, with colloid deposits or deposits of calcium and the formation of cysts, are suggestive of trauma sustained at birth. These lesions may be found in any portion of the brain, but characteristically in the frontal and occipital lobes, in the portions drained by the vena terminalis and the vena lateralis ventriculi and in the basal ganglions. The secondary process may be true encephalitis or pseudo-encephalitis.

CONCLUSIONS

A clinical pathologic syndrome of encephalitis is described in three children of one family in whom the primary condition was apparently of traumatic origin at birth, while the superimposed changes were of infectious or toxic origin.

It is suggested that many of the idiopathic and atypical forms of encephalitis in children are due to the superimposition of a mild infection or intoxication on foci of lowered resistance in the brain, secondary to insults sustained at birth.

Colloid deposits and deposits of calcium in the brains of children are explained as sequelae to injuries sustained at birth.

CONGENITAL VALVES OF THE POSTERIOR URETHRA IN TWINS

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AND
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While the number of reports of congenital valves in the posterior urethra is close to one hundred, we present, for the first time, a description of identical congenital valves in twins.

REPORT OF CASE

An octipara, aged 38, was admitted to the obstetric service of Dr. Charles Newberger on Nov. 9, 1932. All previous deliveries were normal; there had been no twins. At the time of admission the patient was in active labor; the membranes had ruptured about fifteen minutes previously. After the delivery of the first child, it was found necessary to rupture the membranes of the second child. Delivery was uncomplicated. The infants, both boys, weighed 6 pounds and 1¾ ounces (2,771 Gm.) and 5 pounds and 12¼ ounces (2,615 Gm.). Both had undescended testicles, but otherwise appeared normal.

During the first few days the infants presented no abnormalities. On the fifth day the older one showed an excessive gain in weight and an edema of the lower part of the anterior abdominal wall. Two days later the second infant presented the same changes. The urinary bladder was then found distended in both infants, but there was constant though slight dribbling of urine. The bladder formed a globular mass reaching 1 cm. above the umbilicus. The edema extended gradually, involving eventually both the lower extremities and the face. Twitching of the upper extremities was noted on the seventh day. No obstruction was encountered when the infants were catheterized on the seventh day. The urine was clear and normal on chemical and microscopic examination. The catheterizations were repeated on subsequent occasions, and only twice did the catheter meet with some difficulty, but the bladder was entered each time. On the eleventh day of illness an exudate was found in the urine for the first time. The temperature, which had been normal or subnormal for the first eleven days, rose to 100.4 F. in the first child and to 101 F. in the second on the twelfth day after birth, or almost immediately after the exudate appeared in the urine.

There was a leukocytosis of 21,600 in the first baby and 18,200 in the second; 66 per cent were neutrophils and the others lymphocytes. The blood had a marked retention of nitrogenous substances: nonprotein nitrogen, 128 mg. per hundred cubic centimeters in the first child and 137 mg. in the second; urea nitrogen, 96 and 97 mg.; uric acid, 19.5 and 16 mg.; creatinine, 6 and 5.8 mg. The plasma chlorides were 500 mg. and 400 mg., respectively.

Presented before the Chicago Pathological Society, Feb. 13, 1933.

From the Pathological Laboratories and the Obstetrical Department, Mount Sinai Hospital.

Roentgen examination of the spinal column showed no abnormalities. Skiodan was injected intravenously, but neither the kidneys nor the bladder was visualized.

The course was identical in both infants. The younger child died two days before the older one, on the seventeenth day. The clinical diagnosis was: genito-urinary abnormality and uremia.

The younger infant was examined eighteen hours after death. The body was well developed. Both testicles were in the inguinal canals. There was marked edema of the anterior abdominal wall, thighs and scrotum. The abdomen was markedly distended. The urinary bladder was 4 by 3.5 by 3 cm. The wall was greatly hypertrophied and 7 mm. thick. The mucosa was pale and moderately trabeculated. The lumen was filled with a cloudy, purulent urine. The ureteral orifices were patent. The posterior urethral orifice was markedly widened, and the dilated posterior urethra formed a continuation of the urinary bladder. The wall of the prostatic portion of the posterior urethra was hypertrophied and about 5 mm. thick. A probe was introduced into the posterior urethral orifice, but met with an obstruction after a short distance. When the same probe was introduced through

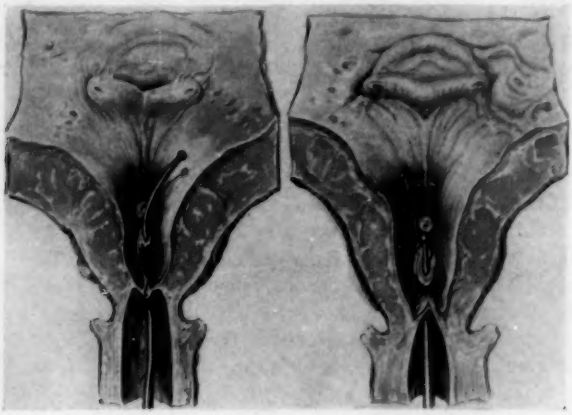

Fig. 1.—Drawing showing the trigon of the hypertrophied urinary bladder with the ureteral orifices, the posterior urethra, the enlarged colliculus seminalis, the utriculus and the valves, of each twin. Probes were introduced through the openings of the valves.

the anterior urethral orifice, it easily entered the urinary bladder. Water was introduced into the anterior urethral orifice by a syringe and cannula. It entered the urinary bladder in a continuous stream through the posterior urethral orifice. On reversal of the procedure, by introducing the cannula into the posterior orifice, no water appeared through the anterior orifice, even with considerable pressure. The urethra was then opened along its dorsal surface to the point of obstruction, which was due to a pair of mucosal valves extending from the anterior aspect of the enlarged and elevated colliculus seminalis (fig. 1). The valves extended distally on each side toward the lateral and anterior wall, and united at the top, thus encircling the entire circumference of the urethra and leaving as a communication a narrow slit in the center. In the fresh specimen the slit was hardly visible, but was readily demonstrable with a probe. In the hardened specimen the opening became exaggerated, owing to the presence of a probe during the process of hardening. The valves appeared ballooned out, with the convexity facing anteriorly.

The utriculus prostaticus and the openings of the ejaculatory ducts were present in their normal location on the colliculus seminalis. The urethra anterior to the valvular obstruction had no abnormalities. The testicles, prostate and seminal vesicles were unchanged. The ureters were tortuous, distended with a cloudy yellow fluid and 22 mm. in circumference (fig. 2). The right kidney weighed 45 Gm. It was soft and fluctuating. The capsule stripped with slight difficulty, owing to numerous subcapsular and parenchymal abscesses. On the surfaces made by cutting the normal structures were obscured by abscesses. The renal pelvis and the calices were dilated and distended with a thick purulent fluid. The mucous membrane was thickened and dull and had a few hemorrhages. The left kidney weighed 25 Gm. It presented changes similar to those in the right kidney, though not so advanced. The entire retroperitoneal space contained con-

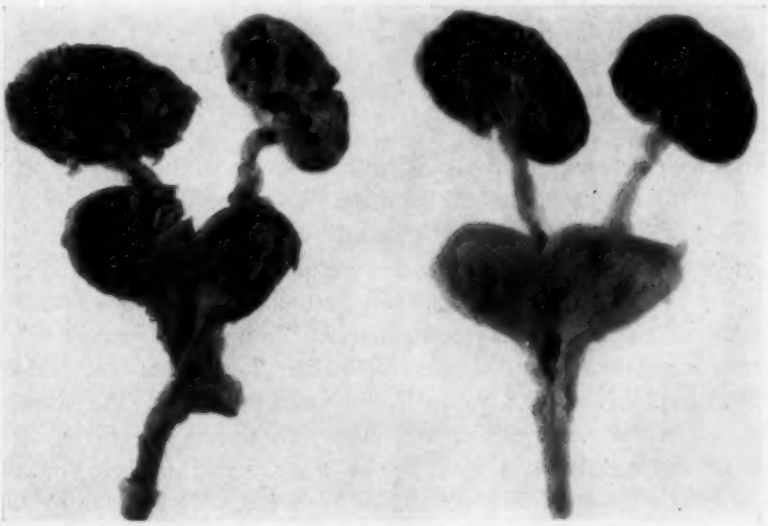

Fig. 2.—Photograph of the kidneys, ureters, urinary bladders and urethras of the twins, showing identical changes in both. The abscesses in the kidneys, the dilatation and tortuosity of the ureters and the hypertrophy of the urinary bladders are marked.

siderable quantities of a thick yellow exudate which surrounded the kidneys and suprarenal glands and extended to the diaphragm.

Histologic sections from the kidneys showed bacterial plugs in the tubular lumens as well as in the capillaries and arterioles. Smears and cultures from the urine and from the exudate in the kidneys and in the retroperitoneal space demonstrated Staphylococcus albus.

Numerous abscesses, ranging from 1 to 5 mm. in diameter, were found in the heart under the epicardium and endocardium and in both lungs. The other organs, including the brain, showed no significant changes. The anatomic diagnosis was: congenital valves of the posterior urethra, hypertrophy and dilatation of the prostatic urethra and the urinary bladder, acute ascending cysto-ureteropyelonephritis, pyonephrosis, acute suppurative perinephritis and pyemia.

In the body of the second infant there was a larger quantity of exudate in the retroperitoneal space. The kidneys were about 10 Gm. heavier on each side, and the ureters were somewhat less distended, but otherwise the changes were identical in every respect with those in first infant.

COMMENT

Various attempts have been made to classify valvular obstructions in the posterior urethra. The modern and popular classification by Young [1] considers three varieties: 1. One or two semilunar folds extending anteriorly from the verumontanum toward the penile urethra. 2. Such folds extending posteriorly from the upper edge of the verumontanum. This type is quite rare. 3. The iris valve, bearing no relation to the verumontanum, attached to the entire circumference of the urethra with a small opening near the center. This variety is extremely rare.

While it is generally agreed that the iris valves develop from persistent portions of the urogenital diaphragm, analogous to the anal and hymenal membranes, there is a great diversity of opinion as to the pathogenesis of the other two varieties. For a review of the different opinions, the reader is referred to the article of Kretschmer and Pierson.[2]

It is probable that there is a different developmental mechanism involved in the different types. The valvular obstructions which are included in the first and second group of Young have in common the convergence toward the colliculus seminalis. They seem best explained by the hypothesis of Lowsley,[3] who suggested that the abnormal implantation of the wolffian and müllerian ducts into the posterior wall of the urogenital sinus may be instrumental in bringing them about. As a result of their normal implantation, they form an elevation on the floor of the prostatic portion of the urethra, the colliculus mülleri, which later becomes the colliculus seminalis or the verumontanum. The urethral crest, which is a continuation of the colliculus seminalis, bifurcates normally and forms very fine ridges running toward the lateral walls of the posterior urethra. In case of a lower implantation of the ducts, the colliculus, as well as the urethral crest, becomes more prominent. It is possible that occasionally the prominence of the crest and of its two arms may assume the proportions of mucosal folds which extend along from the posterior on the lateral, and eventually even on the anterior, wall of the urethra. The lateral or anterior insertion may end at any imaginable level, and in extreme cases a union may result, with the formation of a central slitlike opening of various

1. Young, Frontz and Baldwin: J. Urol. **3**:289, 1919.
2. Kretschmer, H. L., and Pierson, L. E.: Am. J. Dis. Child. **38**:804, 1929.
3. Lowsley: Am. J. Anat. **13**:299, 1912; Ann. Surg. **60**:733, 1914.

shapes and dimensions. In the further course the folds become exaggerated as a result of urinary pressure and assume the shape of valves.

The valves which run posteriorly from the colliculus seminalis toward the urinary bladder may be similarly explained as those running anteriorly, by the assumption that originally they also run anteriorly, but change their position as a result of the unequal growth of various portions of the posterior urethra, mainly in connection with the growth of the prostate. It is assumed that the posterior wall with the colliculus seminalis grows faster and is carried distally to a greater extent than is the roof of the urethra. Thus under certain, as yet undetermined, conditions the anterior course of the valvular folds may be reversed and directed toward the urinary bladder.

In connection with this hypothesis it is of interest that in all reports of cases with valves running anteriorly or posteriorly from the colliculus seminalis, the latter are reported as more or less markedly enlarged. Thus it appears that it would be justified to combine the two types of valves which Young classified as types I and II. We should like to suggest the term "pericollicular valves of the posterior urethra" for the combined type, and to subdivide the group into the anterior variety, which would correspond with Young's type I, and the posterior variety, which would be identical with type II. Such valves may be unilateral or bilateral.

The iris valves form a separate group, as do also the various forms of horizontal mucosal folds, proximally to or distally from the colliculus seminalis but not at all connected with it. The latter type may originate either from the posterior or from the anterior wall of the urethra, and is less known than the pericollicular variety. It is possible that these cases are more frequent than would appear from the reports in the literature, but rarely give rise to serious symptoms.

The particular interest in our two cases is due to the circumstance that the identical pericollicular valves were found in both twins. The question of the monozygotic or dizygotic nature of the twins cannot be answered because the placenta and membranes were not properly examined. The presence of the identical malformation in both twins can be construed with reasonable justification as favoring their monozygotism. DeLee [4] stated that the same deformity often exists in monozygotic twins. He reported a case of double harelip, and quoted C. E. Black, who saw a pair of twins with a rudimentary colon.

4. DeLee, J. B.: The Principles and Practice of Obstetrics, Philadelphia, W. B. Saunders Company, 1924, p. 496.

CONCLUSION

Identical valves in the posterior urethra were found in twins. They produced an obstruction to the urinary flow, with the usual clinical and anatomic consequences. The clinical picture and the pathologic changes were identical in these twins. The term "pericollicular valves," with an anterior and a posterior subvariety, is suggested to replace types I and II of Young's classification. The modification is based on the apparent anatomic and suggestive embryologic relationships to the colliculus seminalis.

General Review

HYPERPARATHYROIDISM (RECKLINGHAUSEN'S DISEASE OF BONE)

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INTRODUCTION

The Concept of Hyperparathyroidism: Its Evolution.—Von Recklinghausen, in 1891, fully described the changes in the bones in the disease entity (advanced stages) which has since been called generalized osteitis fibrosa cystica or Recklinghausen's disease.[1] He undertook, on anatomic grounds, to distinguish the condition from genuine osteomalacia. He succeeded, for the first time, in drawing a clearcut pathologic picture which definitely differentiated the advanced stage of this disease from osteomalacia. Von Recklinghausen clearly appreciated that cases 5 and 7 of his contribution to Virchow's Festschrift closely resembled those previously described by Engel[2] and by Langendorff and Mommsen.[3] Each of these writers had reported a case of severe deforming osseous disease with cysts and giant cell areas, but they had erroneously interpreted the cases as instances of peculiar forms of osteomalacia. (Clinically, case 7 was considered as one of acute osteomalacia.) Hirschberg,[4] in 1889, also reported a case which he misinterpreted as one of osteomalacia and which, from the description, was clearly one of Recklinghausen's disease. As Hirschberg's case was reported from Dresden (when the institute was under the directorship of Schmorl's predecessor), Schmorl[5] had an opportunity to reexamine the pathologic material, and he recently recorded the fact that the bones undeniably showed generalized osteitis fibrosa cystica and not osteomalacia. It is interesting that more recently Denninger[6] unearthed a skeleton which was estimated as being 1,000 years old, the gross appearance of which suggested that generalized osteitis fibrosa cystica had existed.

1. von Recklinghausen, F.: Festschrift Rudolf Virchow zu seinem 71. Geburtstage, Berlin, G. Reiner, 1891.
2. Engel, quoted by von Recklinghausen.[1]
3. Langendorff, O., and Mommsen, J.: Virchows Arch. f. path. Anat. **69**:452, 1877.
4. Hirschberg, K.: Beitr. z. path. Anat. u. z. allg. Path. **6**:513, 1889.
5. Schmorl, G.: Virchows Arch. f. path. Anat. **283**:694, 1932.
6. Denninger, H. S.: Arch. Path. **11**:939, 1931.

In none of these early cases was any mention made of the condition of the parathyroid glands. It is readily understood why recognition of the parathyroid factor in Recklinghausen's disease came slowly, as these glands were not described as independent anatomic structures until 1880, while any part of their function remained in doubt until 1896. Vassale and Generali at that time, and others after them, showed that removal of the parathyroids—the thyroid gland being left intact—led to tetany. In 1909, MacCallum and Voegtlin [7] and others established parathyroid insufficiency as the cause of this tetany, and found associated with it a fall in the serum calcium and a rise in the serum phosphorus. Greenwald and Gross [8] further established that the total excretion of calcium was less after thyroparathyroidectomy than before.

While the syndrome of hypoparathyroidism (due to removal of the parathyroid glands) was first being investigated, the literature began to indicate that parathyroid enlargement may be found in certain diseases of bone. However, it was fully twenty years before a definite association was established between parathyroid enlargement and Recklinghausen's disease. The first indication in this direction came in 1904 from Askanazy,[9] when he described, under the title "Ueber Ostitis Deformans ohne Osteoides Gewebe," his studies of the bones of a woman 51 years of age who suffered from multiple fractures. He believed that grossly the appearance of the bones suggested osteitis fibrosa rather than Paget's disease, but many of their features reminded him of the case of progressive bone atrophy which he had described in 1901.[10] The pertinent finding in this case was that attached to the left thryroid lobe there was a tumor measuring 4.5 by 2 by 2 cm., which was composed of large cells suggesting suprarenal cortical cells. Askanazy stated that the tumor could have originated in the parathyroid gland. Although he did not specifically suggest a relationship between this apparent parathyroid tumor and the bone disease, in a later discussion of a paper by Weichselbaum [11] he made reference to this case and stated that such a relationship could be surmised. The choice of the title for Askanazy's report of 1904 is most unfortunate, as it creates the impression that the condition was Paget's disease—and this case is still frequently featured in the literature as one of Paget's disease associated with parathyroid adenoma.

It was, however, the classic anatomic and experimental investigations of Erdheim that conclusively focused the attention of pathologists

7. MacCallum, W. G., and Voegtlin, C.: J. Exper. Med. **11**:118, 1909.

8. Greenwald, I., and Gross, J.: J. Biol. Chem. **64**:185, 1925.

9. Askanazy, M.: Arb. a. d. Geb. d. path. Anat. Inst. zu Tübingen **4**:398, 1904.

10. Askanazy, M.: Beiträge zur Knochenpathologie, Festschrift für M. Jaffé, Braunschweig, Vieweg und Sohn, 1901.

11. Weichselbaum, A.: Verhandl. d. deutsch. path. Gesellsch. **10**:83, 1906.

on the possible relationship between abnormalities of the parathyroid glands and disease of bone. He discovered [12] that removal of these glands in rats leads to deficient calcification of the dentin of the incisors. This prompted him to investigate the condition of the parathyroid glands in his cases of osteomalacia.[13] In a case described as one of puerperal osteomalacia, which he reported in 1907, he noted that one of the parathyroids was much enlarged (measuring 4.3 by 3.6 by 0.5 to 1 cm.), while the other three glands showed nothing striking, either grossly or histologically. A question arose in regard to the large gland in this case, as to whether the enlargement resulted from a compensatory hyperplasia or from formation of an adenoma. This is still a topic of much controversy in some phases of the subject of enlarged parathyroid glands. Erdheim inclined to the view that the enlargement was the result of compensatory hypertrophy secondary to the bone disease.

In his report of 1907, Erdheim presented seven additional cases of puerperal and senile osteomalacia, in which careful study of the parathyroids was made. In two cases, gross enlargement of one or more of the glands was found, with what he interpreted as microscopic evidences of hyperplasia. This he found in the enlarged as well as in the normal-sized glands. In the five other cases, no enlargement was apparent; however, in three of them he reported the presence of hyperplasia on histologic grounds. In a previous report he stated that fixing the parathyroids in Altmann's fluid and then treating them with osmic acid were technical details which should be followed in order to make certain of the presence of microscopic hyperplasia.[14] More recently, Bergstrand [15] contested the validity of this method in demonstrating hyperplasia microscopically. In this connection, mention may be made that disappearance of the interstitial fat cells from the parathyroid glands of adults is associated with hyperplasia of these glands, even without discernible gross enlargement.

Thereafter the literature was permeated with reports of enlargement of the parathyroid glands in association with diseases showing lesions of bone, such as Paget's disease, Recklinghausen's disease, osteomalacia, rickets and senile osteoporosis. Parathyroid enlargement was also reported in some cases of multiple myeloma, as well as in certain instances of carcinomatous metastases to the skeleton. In carefully controlled work on experimental rickets in rats, which related the

12. Erdheim, J.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **16**:632, 1906.
13. Erdheim, J.: Sitzungsb. d. k. Akad. d. Wissensch. Math.-naturw. Kl., Wien **116**:311, 1907.
14. Erdheim, J.: Beitr. z. path. Anat. u. z. allg. Path. **33**:158, 1903.
15. Bergstrand, H.: Acta med. Scandinav **54**:539, 1921.

rickets to a calcium-phosphorus imbalance with an added deficiency of vitamin D, parathyroid enlargement was likewise reported.

Furthermore, some degrees of parathyroid enlargement were also reported in a number of senile persons without bone disease. Other authors described enlarged parathyroids associated with paralysis agitans.[16] MacCallum,[17] as early as 1905, had observed a parathyroid gland measuring 2 cm. in a young patient with nephritis, who died of uremia; the bones were not investigated, but may have shown resorption. In addition, a number of reports appeared which indicated that considerable enlargement of a parathyroid was possible even without bone disease. Maresch's case [18] may be taken as a perfect example; among others, he reported in detail a case of parathyroid tumor which measured 7 by 4 cm. by 13 to 17 mm.; the other three parathyroids were normal grossly and microscopically. The striking feature of this case was the lack of evidence in the bones of either active or healed disease. The large tumor was designated as an adenoma of the principal cells; in the capsule of the tumor a small normal parathyroid was seen.

It is plainly evident from the last paragraph that the state of knowledge concerning the relationship of parathyroid enlargement to bone disease soon became much involved. For a time, especially early in the development of the knowledge of this subject, the view more generally accepted was that originally postulated by Erdheim [13] in regard to osteomalacia. He stated that the parathyroid enlargement should be looked on as the result of the bone disease rather than the cause of it; that is, the parathyroid enlargement was secondary. There can be no doubt that Erdheim was quite correct in his view regarding osteomalacia, which also holds for the enlargement of the parathyroid glands, if present, in a number of other conditions, such as multiple myeloma, carcinomatous metastases to the skeleton and rickets. But in time a number of observers began to question whether all parathyroid enlargements were secondary to the bone softening.

Thus, in 1915, Schlagenhaufer,[19] although not quite clear as to the distinctions between Recklinghausen's disease and genuine osteomalacia, suggested, on more or less empirical grounds, that it would be advantageous to attempt the removal of enlarged parathyroid glands in some of the malacic bone diseases. This was apparently the first definite deviation from the theory of compensatory hypertrophy.

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16. Bergstrand.[15] Harbitz, F.: J. M. Research **32**:361, 1915.
17. MacCallum, W. G.: Bull. Johns Hopkins Hosp. **16**:87, 1905.
18. Maresch, R.: Frankfurt. Ztschr. f. Path. **19**:159, 1916.
19. Schlagenhaufer: Wien. klin. Wchnschr. **28**:1362, 1915; Off. Protokoll, d. K. K. Ges. d. Aerzte, Wien., Sitzb. Dec. 3, 1915.

In discussing Schlagenhaufer's paper, Maresch stated that an investigation of the parathyroid glands in twenty-three cases of various malacic diseases of the skeleton revealed ten cases of genuine osteomalacia in which the parathyroids were slightly or not at all involved. In the instances of pronounced senile bone atrophy, the condition of the parathyroids was similar. Three of the twenty-three cases showed significant parathyroid enlargements. Two of these were undoubtedly instances of Recklinghausen's disease. Maresch, in this discussion, supported Schlagenhaufer's suggestion that removal of the parathyroids should be attempted for therapeutic purposes in some of the malacic diseases.

In 1923, Dawson and Struthers,[20] reporting a case of generalized osteitis fibrosa with a principal cell adenoma of the parathyroid gland and extensive metastatic calcification of many organs and tissues, suggested that a cause and effect relationship may have existed between the adenoma and the bone changes. About this time literature on pathology contained several other reports in which this view was expressed.

The subject rested at this stage until about 1925, when several significant advances in parathyroid physiology were made. These were of utmost importance in finally clarifying the relationship between parathyroid enlargement and Recklinghausen's disease. At this time, the preparation by Hanson [21] and Collip [22] of active extracts of parathyroid glands [23] permitted experimental study of the effects of injection of the extracts. Furthermore, Mandl [24] discovered that removal of a parathyroid adenoma in generalized osteitis fibrosa cystica (Recklinghausen's disease) resulted in marked immediate clinical improvement of the patient, with diminution of the urinary excretion of calcium. Before reaching the happy conclusion in his case (that of a bed-ridden patient), Mandl, still under the influence of the Erdheim hypothesis of compensatory hyperplasia, had attempted homoplastic transplantation of the parathyroids, but this led to aggravation of the clinical symptoms. Thus, he was the first to give definite clinical proof that the bone changes in cases of osteitis fibrosa cystica were caused by a disturbed parathyroid function. Mandl's observations were soon confirmed and his conclusions widely accepted. A rapidly increasing series of reported cases, of which there are now about forty, have been brought forward to support the hypothesis of parathyroid hypersecretion. It is not my

20. Dawson, J. W., and Struthers, J. W.: Edinburgh M. J. **30**:421, 1923.

21. Hanson, A. M.: Mil. Surgeon **54**:76, 218 and 554, 1924.

22. Collip, J. B.: J. Biol. Chem. **63**:395, 1925; Medicine **5**:1, 1926.

23. The Collip extract is manufactured by Eli Lilly & Co. and sold under the trade name "parathormone."

24. Mandl, F.: Arch. f. klin. Chir. **143**:1 and 245, 1926; Zentralbl. f. Chir. **56**:1739, 1929.

purpose to consider separately each reported case; most of these contributions have been important in formulating a fuller conception of the various aspects of this disease.[25]

The effects of the injection of parathyroid extract-Collip, especially in animals, were soon intensively investigated. It was shown that in susceptible animals, particularly dogs, small nontoxic doses raised the serum calcium and caused an increased excretion of calcium and phosphorus through the urine. Toxic doses of parathyroid extract raised the serum phosphorus in addition, caused urinary suppression, and rapidly led to the death of the animal. In time also, the effect of injection of parathyroid extract in man was investigated. Albright, Bauer, Ropes and Aub,[26] studying the effects of the administration of parathyroid extract-Collip on patients given an inadequate calcium diet, found a gradual increase of the urinary excretion of calcium but unaffected fecal excretion. The calcium level in the blood was gradually, but markedly, elevated. The extent of elevation of serum calcium varied in different persons, and was more marked when the patient was on a diet high in calcium. The injections of parathyroid extract also abruptly

25. It is finally of interest to mention here that a number of reported cases of osteomalacia with parathyroid adenoma have since been shown to have been cases of Recklinghausen's disease. Even such a master of bone pathology as Schmorl had permitted cases of Recklinghausen's disease to be reported from his institute by Hart (Beitr. z. path. Anat. u. z. allg. Path. **36**:353, 1904) and Molineus (Arch. f. klin. Chir. **101**:333, 1913) as instances of osteomalacia. Recently, Schmorl put himself on record as withdrawing their diagnoses of osteomalacia, stating that these cases were examples of Recklinghausen's disease.[5] Molineus' three instances were reported in 1913, and each of the patients had a parathyroid adenoma. It is obvious from the foregoing statements that the literature still abounds in reports of cases purporting to be cases of osteomalacia which are palpably examples of Recklinghausen's disease. This is more especially so in cases in which cysts and giant cell tumors have been described with or without the presence of parathyroid adenomas.

In fact, it is possible that the first case in which there was an associated enlarged parathyroid gland reported by Erdheim[13] in 1907 may have been one of Recklinghausen's disease rather than of osteomalacia. In this case the changes were most extensive in the pelvis, but only the calvarium, vertebrae and ribs were submitted to histologic examination. Erdheim stated that the marrow of the calvarium was very fibrous, while the osteoid borders of all the bones examined were very narrow; numerous osteoblasts were present. The very narrow osteoid borders, the fibrous marrow and the large numbers of osteoblasts would seem to militate against an absolute diagnosis of osteomalacia. It is true, this patient's condition was aggravated by pregnancy, and a diagnosis of puerperal osteomalacia seems supported by this fact. However, my colleagues and I have shown, in unpublished expjeriments with injections of parathyroid extract-Collip that severe lesions of hyperparathyroidism develop with smaller doses in pregnant guinea-pigs and rats than in nonpregnant animals; in fact, such animals usually die of acute hyperparathyroidism following doses that do not kill nonpregnant animals.

26. Albright, F.; Bauer, W.; Ropes, M., and Aub, J. C.: J. Clin. Investigation **7**:139, 1929.

increased the urinary excretion of phosphorus without affecting the fecal excretion. The phosphorus level in the blood was primarily lowered by parathyroid extract. With toxic effects of parathyroid extract the urinary phosphorus fell, and the serum phosphorus rose. Essentially, all these effects were observed earlier by Greenwald and Gross [27] in the metabolic studies with parathyroid extract-Collip which they carried out in dogs. In this connection, it is interesting to note the observation by Hannon, Shorr, McClellan and DuBois [28] that all the symptoms in their patient with Recklinghausen's disease were aggravated on injection of parathyroid extract-Collip.

Barr and Bulger,[29] recognizing the similarity between many of the clinical and chemical effects that result from the experimental injection of parathyroid extract-Collip in man and animals and the clinical and chemical features of Recklinghausen's disease, were the first to apply the term "hyperparathyroidism" to clinical Recklinghausen's disease.

Although extensive studies of the effects of acute and chronic experimental hyperparathyroidism were carried out after Collip's preparation of an active parathyroid extract, none of the investigators submitted the bones of their animals to complete examination. My colleagues and I,[30] between 1930 and 1932, were the first to report the effects of acute and chronic experimental hyperparathyroidism on the histologic appearance of the bones of animals. In addition, we reported certain chemical phases of our work.[31] The studies were carried out on dogs, guinea-pigs and rabbits. The dog is most susceptible to the effects of hyperparathyroidism and readily shows changes in the bones and in the blood, while the rabbit is relatively very resistant to the effects of parathyroid extract-Collip. Therefore, the rabbit is not especially satisfactory for the pursuit of such studies.[30e]

These experiments showed that many, if not all, of the pathologic changes observed in the bones in Recklinghausen's disease are produced in experimental hyperparathyroidism in susceptible animals. The studies brought to light irrefutable evidence that hyperparathyroidism was, in the main, responsible for the pathologic changes of Recklinghausen's disease. Thus the parathyroid enlargements—the adenomas—in association with Recklinghausen's disease were established as the direct cause of the bone changes.

27. Greenwald, I., and Gross, J.: J. Biol. Chem. **64**:217, 1925.

28. Hannon, R. R.; Shorr, E.; McClellan, W. S., and DuBois, E. F.: Clin. Investigation **8**:215, 1930.

29. Barr, D. P., and Bulger, H. A.: Am. J. M. Sc. **179**:449, 1930.

30. (*a*) Jaffe, H. L., and Bodansky, A.: J. Exper. Med. **52**:669, 1930. (*b*) Jaffe, H. L.; Bodansky, A., and Blair, J. E.; (*c*) Arch. Path. **11**:207, 1931; (*d*) J. Exper. Med. **55**:139, 1932; (*e*) ibid. **55**:695, 1932.

31. (*a*) Bodansky, A.; Blair, J. E., and Jaffe, H. L.: J. Biol. Chem. **88**:629, 1930. (*b*) Bodansky, A., and Jaffe, H. L.: J. Exper. Med. **53**:591, 1931; (*c*) J. Biol. Chem. **93**:543, 1931.

Some aspects of this work have since been confirmed by Johnson [32] and by Abeloff and Sobel.[33] Rutishauser [34] stated that he produced considerable resorption and fibrosis of the bones of rabbits inoculated with mashed human parathyroid glands, obtained post mortem. In view of the marked resistance of rabbits to even huge doses of parathyroid extract-Collip, his results are surprising and would be important if confirmed. Johnson's results in experiments with dogs completely duplicate the findings reported by Bodansky and me. His experiments with rats show that rats suffering from severe hyperparathyroidism, after short periods of treatment, manifest all the histologic reactions seen by us following the injection of parathyroid extract-Collip in dogs and guinea-pigs. However, the roentgenograms and microscopic sections of the long tubular bones of the rats kept longest on parathyroid extract show plainly the development of a metaphyseal osteosclerosis which Johnson failed to discuss. It is interesting, in this connection, that Bauer, Aub and Albright [35] had noted grossly that in the growing rat the administration of parathyroid extract-Collip (885 units over a hundred and ten days), resulted in diminution of the length of the bones and in an increase of the number of trabeculae. My colleagues and I [36] have found that in rats which are fed on an edequate diet or one high in calcium (a diet which gives satisfactory growth of bone) and which are given injections of parathyroid extract-Collip over long periods of time, an extensive metaphyseal osteosclerosis develops which in many ways resembles the osteosclerosis following the ingestion of elementary phosphorus. This osteosclerosis is interpreted as a healing phenomenon associated with a compensation to the injection of parathyroid extract. We observed compensation to the prolonged injection of parathyroid extract-Collip in all species studied, but considered this problem specifically in relation to the guinea-pigs.[30d]

Recently, Dr. David Shelling, of the department of pediatrics of Johns Hopkins Hospital, showed me a slide from a long tubular bone of a rat given parathyroid extract-Collip and fed on a diet high in calcium; this bone showed osteosclerosis. Selye,[37] in a recent paper, also observing the osteosclerosis induced by injection of parathyroid extract-Collip, attempted to correlate these changes with those of the marble bone disease described by Albers-Schönberg. He suggested that this disease might be due to a special form of hyperparathyroidism. I am firm in the belief that there is, in such experiments, no basis for asso-

32. Johnson, J. L.: Am. J. M. Sc. **183**:761 and 769, 1932.
33. Abeloff, A. J., and Sobel, I. P.: Arch. Path. **14**:471, 1932.
34. Rutishauser, E.: Centralbl. f. allg. Path. u. path. Anat. **53**:305, 1931-1932.
35. Bauer, W., Aub, J. C., and Albright, F.: J. Exper. Med. **49**:145, 1929.
36. Unpublished experiments.
37. Selye, H.: Endocrinology **16**:547, 1932.

ciating Albers-Schönberg disease with hyperparathyroidism. Selye ascribed the new bone formation in chronic hyperparathyroidism in rats to an osteoblastic stimulation induced by parathyroid extract-Collip. Our own experience, however, is that the new bone formation is a healing phenomenon in an animal that has compensated itself in adjustment to the state of hyperparathyroidism and in which bone resorption and new bone formation are still actively in progress.

GENERAL PATHOLOGY

Range of Changes in Bone.—Before entering into a description of the osseous changes of Recklinghausen's disease, it is advisable to point out that this disease is quite rare. Furthermore, it develops more or less progressively over a period of years, and certain important factors may enter to influence and modify the pathologic picture. These factors comprehend the age of the patient, the varying degrees of activity and secretion of the enlarged parathyroid, the character of the diet (acid or basic), the effects of complete or incomplete fracture, the duration of the disease prior to the study of the bones, the complications that conditions such as pregnancy would involve, etc.

The pathologic appearance of the osseous system may range from an advanced picture such as von Recklinghausen described, and to which the designation of generalized osteitis fibrosa cystica may rightfully be given, to one in which the lesions are so slight that they are almost indistinguishable grossly, such as that in the case described by Bergstrand.[38] In this case the bones showed microscopic evidences of active resorption, with numerous osteoclasts in somewhat enlarged haversian canals; there was an increase in connective tissue in these canals and about the bone trabeculae, but the major marrow cavities of the bones showed practically unchanged contents; there were no evidences of new bone formation, and cysts and giant cell tumors were absent. Furthermore, during life, the patient had many symptoms of hyperparathyroidism, and at autopsy two prune-sized parathyroid adenomas were found. Such cases may more rightfully be looked on as instances of progressive atrophy of bone or as cases of a form of osteoporosis caused by hyperparathyroidism.[39]

38. Bergstrand, H.: Acta med. Scandinav. **76**:128, 1931.

39. Later it will be shown, on the basis of comparative clinical and experimental material, that what Askanazy,[10] Pick (Berl. klin. Wchnschr. **54**:797, 1917), Schmorl (Verhandl. d. deutsch. path. Gesellsch. **21**:71, 1926) and Bodansky, Blair and I [30c] have conceived of as progressive bone atrophy is the result of a progressive resorption and scarring of the bone with the prevailing of resorptive phenomena over the reparative reactions. The dissecting resorption of trabeculae is present both in advanced Recklinghausen's disease and in progressive bone atrophy, and is to be found especially in the spongiosa. Our experimental results on guinea-pigs show that all the features of progressive bone atrophy may be produced by chronic hyperparathyroidism.

When I state that hyperparathyroidism may produce the microscopic picture of osteoporosis, it is to be understood that I do not refer to the osteoporosis that occurs in senile atrophy or atrophy due to inactivity. In such conditions, the compact and the spongy bone become thin, but remain smooth. There is virtually no fibrous invasion of the haversian canals and the intertrabecular spaces. Rarely, some fibrous transformation occurs in association with senile atrophy and that due to inactivity, but it is never extensive. Thus, in designating Bergstrand's case as one of osteoporosis, the distinction is drawn between it and senile osteoporoses or those due to inactivity. This case is one of osteoporosis only in the sense that there had been resorption and some scarring of bone and marrow without transformation of its general architecture or much new bone formation. Hyperparathyroidism was plainly the initiating factor.

Between these two extreme types (generalized osteitis fibrosa with cysts and giant cell tumors, on the one hand, and progressive bone atrophy or osteoporosis on the other) are cases showing various degrees of implication and various stages of involvement of the different bones of the same patient. Thus, Dawson and Struthers'[20] case, in which many of the bones presented the classic evidences of Recklinghausen's disease (with cysts, giant cell tumors and extensive fibrosis of the major marrow cavity), showed no gross evidence of disease in the left femur. However, on microscopic examination, this bone displayed a very early stage of involvement. Microscopically, the haversian systems throughout the compacta were enlarged, while the trabeculae of the spongy bone were thin and the intertrabecular spaces were greatly widened; the normal fatty marrow within the major marrow cavity was practically unchanged. The enlarged haversian spaces of the compacta contained loose, vascular, fibrocellular tissue of varying amounts, with osteoclasts; they showed every transition in size from minimal enlargement to large irregularly contoured spaces. The entire middle third of the shaft cortex was undergoing this rarefaction, but nowhere on the walls of these canals was any new bone being deposited. Thus, in Dawson and Struthers' case, the changes in the left femur were in every respect identical with those existing in many bones in Bergstrand's case. The changes in the left femur are to be considered as incompletely advanced stages of the evolution of the disease; they help considerably in understanding many features of the pathogenesis of the disease picture.

On the other hand, in Schupp's[40] case there is shown a pathologic picture even further advanced than that described in the left femur in the case just cited. It is striking and important because no giant cell tumors or cysts were grossly present in any of the bones, although

40. Schupp, H.: Deutsche Ztschr. f. Chir. **233**:95, 1931.

there had been extensive resorption and transformation of the original bony architecture with new bone formation. The patient was a woman, 51 years of age, who gave a history of progressive weakness taking place over a period of five years. At autopsy there were found multiple fractures in the upper portion of the right femur, with transformation of the architecture of the skull, vertebrae, pelvis and other bones. Within the substance of the right thyroid lobe there was a parathyroid adenoma, measuring 1.5 by 0.5 by 0.75 cm., which, on histologic examination, was composed of principal cells. The bones showed resorption, with osteoclasts in Howship's lacunae, fine fibrous tissue transformation of the resorbed areas and deposition of lamellar osteoid bone with osteoblasts. As proof that the case was not one of osteomalacia, it is stated that osteoid borders were not present on the surfaces of any of the original bone seen in the sections.

No giant cell tumors were observed grossly or microscopically in any of the bones, although one pigmented area containing giant cells was found grossly in the body of the ninth dorsal vertebra, and nests of cells containing blood pigment were seen microscopically in other bones. Supported by his teacher, Schmorl, Schupp emphasized, as had others, that the presence of giant cell tumors and cysts is not essential in making a diagnosis of Recklinghausen's disease. However, in his own case he believed that fracture of the femur had occurred at the site of a former cyst, all vestiges of which had disappeared by the time the bone was studied at autopsy.

This is exactly the view that we have always held; some of our publications [41] strongly emphasized this, even before Schupp's paper. In our work we stressed the belief that in experimental hyperparathyroidism, decalcification of bone is produced primarily. This may become pronounced and, with the consequent changes, may result in a pathologic picture that simulates the bone changes of clinical Recklinghausen's disease. The other features of the completed pathologic picture of chronic hyperparathyroidism in regard to the bone—that is, the proliferation of the marrow connective tissue, the numerous osteoclasts and Howship's lacunae, the appearance of new bone trabeculae in the connective tissue replacing the original bone, the marrow hemorrhage and giant cell tumor formation, the numerous small and some large cysts and even fractures—are wholly dependent on and consequent on such decalcification. This is also true of any healing phenomena.

By indicating that primary decalcification is the condition on which all the subsequent changes are superimposed, we do not imply that an appreciable interval of time exists between the decalcification and the appearance of any secondary phenomena. Furthermore, while many features other than initial decalcification were enumerated for the

41. Jaffe and Bodansky.[30a] Jaffe, Bodansky and Blair.[30c]

entire osseous picture of chronic experimental hyperparathyroidism, certain of them are more important and appear quite regularly with the progressive decalcification. These are the appearance of osteoclasts and Howship's lacunae and the proliferation of the marrow connective tissue. Others occur less constantly, occur in varying degrees, and are much more dependent on complications for their manifestation—these are giant cell masses following marrow hemorrhage and cysts.

From the foregoing facts one deduces that most of the essential features of the pathologic changes in the bones in cases of clinical hyperparathyroidism are secondary to a rapid decalcification of the skeleton, induced by the hypersecreting parathyroid adenoma or adenomas. The final pathologic picture is modified by, and varies with, the age of the patient, the duration of the disease, the intake and availability of mineral salts, the speed and degree of decalcification and the stresses, strains and possible injuries to which the decalcified skeleton is subjected. It seems fair to conclude, then, that investigators are becoming fully aware of the all-inclusive range of the pathologic changes of hyperparathyroidism. With this knowledge as a starting point (and with the additional accumulating evidence that removal of the hypersecreting parathyroid tissue causes interruption of the course of the disease and often permits considerable healing), there is a real prospect that the severe deforming processes, such as were originally described by von Recklinghausen, will disappear completely because of early diagnosis. One is encouraged in this view by the fact that the chemical changes produced in the body by parathyroid hyperactivity can be detected by chemical study of the blood and of the excretions of such patients and clinical diagnosis thereby greatly aided.

Distribution of Changes in Bone.—In von Recklinghausen's case 7 (a very advanced case), while the disease to some degree involved practically the entire skeleton, the changes were most pronounced in certain bones and bony parts. The long tubular bones showed the greatest degree of change and transformation (closely followed by the spine, including the sacrum, pelvis, skull, jawbones and thoracic flat bones). On the other hand, the short tubular bones, such as the metatarsal and the basal and middle phalanges, showed only the mildest degrees of transformation. The tarsal bones were even less transformed; they were highly porotic, the trabeculae being extremely thin and the intertrabecular marrow quite fatty.

With regard to the long tubular bone, the greatest amount of transformation and new bone formation, in a very advanced case, is usually found in the diaphysis. In von Recklinghausen's case, the extreme ends of both tibias and the lower end of the right femur showed limitation of the disease to the region near the former epiphyseal-diaphyseal junctions. The portions near the articular cartilages were only greatly

porous, the cancellous spaces still containing fatty marrow. In bones which were very extensively diseased, such as the radii, fibulae, left humerus and upper portion of the right femur, the spongy trabeculae of the ends of the bone beneath the articular cartilages were of more or less normal texture. Von Recklinghausen stated that the relative freedom of the epiphyseal ends from involvement by fibro-osteoid tissue was especially noticeable in the metatarsal and phalangeal bones, in which the disease was practically limited to the cortex, while the marrow cavity contained the normal fatty marrow.

It is interesting that when Bodansky, Blair and I [42] made a survey of bone lesions appearing in experimental chronic hyperparathyroidism, we found that the severity and the distribution of these lesions followed, to a great degree, the same pattern of involvement as indicated in the advanced clinical case just cited. The striking feature of this similarity in distribution is that von Recklinghausen's patient was an adult, while the experimental studies were carried on in young, growing animals.

In an attempt to understand such localization, we made a study of the embryogenesis and postnatal development of the skeleton. Our analysis indicated that the most pronounced resorption of bone in experimental hyperparathyroidism occurs in certain sites of predilection, and that the greater susceptibility of these sites may be related to their rate of bone formation. We found that the tarsal and carpal bones and the epiphyses of young guinea-pigs are sites of relatively slow growth. The general principle that we propounded was that the sites of most active bone formation are the sites most susceptible to resorption. Thus, the portions of the skeleton most susceptible to decalcification are those in which formation of bone is most active.

The pronounced susceptibility to resorption (as a result of hyperparathyroidism) of the spongy bone of the metaphyses thus becomes intelligible, especially the spongy bone of the metaphyses of the rapidly growing long tubular bones, of the costochondral junctions, of the cortices of the shafts, particularly near the former epiphyseal cartilage plates, of the cortices of the ribs used most in the respiratory act and of the bones of the skull and lower jaw. This conception offers an explanation as to why the metaphyses of the slower growing short tubular bones showed relatively little evidence of resorption, while the cortices of the shafts of these bones showed practically no evidence of resorption. At the same time, the spongy bone of all epiphyses and of the tarsal and carpal bones, when subjected to conditions producing the lesions described, showed at the most only generalized thinning.

Furthermore, this conception clarifies the greater susceptibility to parathyroid extract noted in the skeletons of actively growing young guinea-pigs compared with the skeletons of adult guinea-pigs. It also

42. Jaffe, H. L.; Bodansky, A. and Blair, J. E.. Arch. Path. **12**:715, 1931.

explains the quantitative differences in the response of different bones and of different portions of given bones in animals treated with parathyroid extract. These differences are observed strikingly in young animals, but also to a certain degree in older ones.

The quantitative relation of resorption of bone to the rate of growth in particular sites may be further extended to include endosteal and periosteal resorption. In young, rapidly growing animals, with the shafts of tubular bones increasing in diameter, the marked degree of subperiosteal resorption that is observed in experimental hyperparathyroidism corresponds to the rapid growth in the subperiosteal regions in the normal animal. In the older animal, in which, normally, subperiosteal growth is greatly diminished, subperiosteal resorption is correspondingly less marked, while subendosteal resorption becomes by far the more prominent factor.

Thus, on the basis of our experimental work we have been able to show that in hyperparathyroidism there is a greater tendency for certain bones to be involved than others; and, finally, that those bones which show a great tendency toward involvement evidence the severest involvements in certain sites of predilection. In addition, it must be considered that in both experimental and clinical hyperparathyroidism an apparent discrepancy in the degree of involvement may exist between two bones (such as the femora) which, on the basis of the conception stated, should be equally involved. The difference may logically be attributed to the association of complicating factors, such as infractions or fractures, or the favoring of bones that would result in more pronounced disease of the bones of the unfavored extremity.

SPECIFIC PATHOLOGY

Appearance of a Long Tubular Bone With Advanced Disease.—In any specific case of Recklinghausen's disease, many bones may be extensively diseased, or a few bones may be greatly diseased while others disclose evidences of only microscopic involvement; finally, there are cases in which the bony lesions are discovered only by the aid of the microscope. It is manifestly impossible to describe minutely each degree of pathologic change to which the bones may be subjected in this disease. The description must be limited to certain degrees of gross variation.

When an extensively involved long tubular bone is examined, the transverse diameter is usually found expanded at some point, sometimes in several places. If the bone is the femur, a considerable degree of coxa vara may be present. The details of the gross appearance may be modified by the presence of recent or healed fractures which create local deformities or very extensive deformation of the bone. The deformation may be so pronounced as to result in a snakelike form similar

to that described in the older publications on osteomalacia. The periosteum surrounding a bone with such an advanced lesion is usually thin; it participates in the general atrophy of tissue that occurs in this disease. If there is any periosteal reaction—which is rare—it is likely to be found in the vicinity of fractures or in regions in which the bone needs reinforcement because of the presence of a cyst or giant cell tumor that is insidiously undermining the integral structure of the bone (the subperiosteal new bone formation being an effort at repair or strengthening). However, even with the expansion of bone attendant on the presence of cysts or giant cell tumors, the overlying periosteum is most likely to evince no reaction.

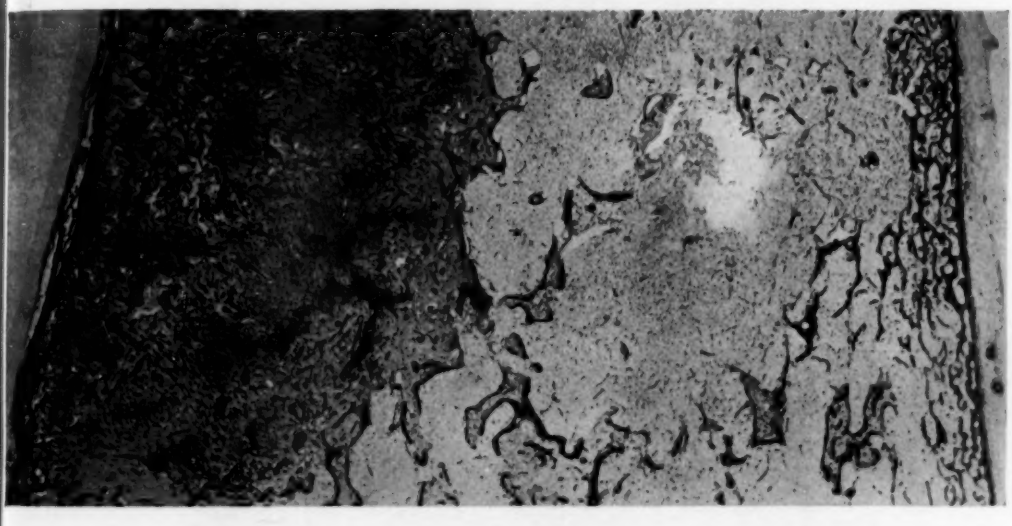

Fig. 1.—A longitudinal section through the diaphysis of a long tubular bone; the periosteum is thin; the major medullary cavity shows a fibrous focus on the left, in which newly formed bone is evident; the rest of the marrow is fatty (right); the original cortex on the right is thin, owing to marked resorption; on the left it is to a considerable degree replaced by the fibrous focus; × 4.

Longitudinal section (a severely involved bone may even be cut with a knife) will disclose almost a complete change from the normal structure of the bone (fig. 1). The major medullary cavity may show considerable replacement of the original tissue by scattered, grayish-white, fibrous foci in which finely reticulated bone may be felt. The marrow cavity may be traversed by single and multilocular cystic spaces which can extend beneath the periosteum. In and between such cystic spaces, recent and old hemorrhage may be present, as well as brownish discolored areas (giant cell tumors). Other areas of the marrow may be fatty or myeloid. In the extreme upper and lower ends of such a

bone, the spongiosa and the intervening cancellous marrow usually manifest the least amount of pathologic deviation; in such areas the bony trabeculae are extremely atrophic. The intertrabecular marrow is fatty; fibrous foci such as are seen in the diaphysis are usually absent. However, immediately beneath the articular cartilage, a slight amount of marrow fibrosis and new bone formation may sometimes be observed; that is, the subchondral spongiosa may be converted into a fine spongy condensed mass of new bone.[43] When the subchondral changes are not

Fig. 2.—The extreme (epiphyseal) end of a long tubular bone; the bony trabeculae are extremely atrophic; the intertrabecular marrow is fatty; × 4.

43. Such subchondral conversion is frequently observed in the bodies of the vertebrae where the spongiosa immediately beneath the usually expanded intervertebral disks is likely to be more or less uniformly condensed. The subchondral spongiosa in the bodies of the vertebrae in Recklinghausen's disease is strikingly different from that observed in Paget's disease. In the latter, the new, spongy trabeculae (of affected bone) are irregularly placed and thickened, closely set or widely separated. They are never as regularly condensed as in Recklinghausen's disease (fig. 5).

obvious grossly, microscopic examination may still reveal the presence of small amounts of fibrous marrow and collections of giant cells in the vicinity of the bony end-plate, sometimes with its complete destruction. Under such circumstances, fibrous tissue, giant cells and newly formed bone may extend into the articular cartilage. The articular cartilage is entirely passive in this disease (figs. 2 and 3).

The original cortex may undergo tremendous change—even to the extent of being completely replaced. Whatever may remain of the original cortex is always thin, owing to marked resorption. It shows a very porous structure, and the resorption may advance to such a pro-

Fig. 3.—A higher power magnification of area shown in figure 2. The subchondral spongiosa reveals microscopically the presence of small amounts of fibrous marrow in the vicinity of the bony end-plate; there is slight new bone formation on a resorbed trabeculae; × 125.

nounced degree that only a thin layer of bone denotes its presence. As the resorption and transformation of the cortex proceed, newly formed bone is deposited. The fibrous foci within the medullary cavity containing the reticulated bone merge in places with the newly formed cortical bone so that the demarcation between cortex and medulla may be completely obliterated.

It is to be noted that the pathologic appearance of such a bone has resulted from a transformation of most of the original bony architecture, with its replacement by large amounts of fibrous tissue in which

poorly calcified new bone forms. In addition, whatever original bone remains has become markedly atrophic.

On microscopic examination, the appearance of connective tissue fiber bone in the fibrous foci within the medullary cavity may be observed. The final conversion of some of these newly formed bony trabeculae into rather immature lamellar bone may also be traced. The new bone formation is the result of metaplasia of osteoblastic connective tissue into bone. The trabeculae of the newly formed fiber bone fuse to produce a reticulum on which lamellar bone formation proceeds as in endochondral ossification. In Recklinghausen's disease there is a great tendency toward the rapid resorption of this newly formed bone; therefore numerous osteoclasts are observed in lacunae on the surfaces of such bone trabeculae or about small fragments of excessively resorbed trabeculae. Furthermore, large areas of connective tissue formation in which no bone appears may also be seen. In such fibrous foci, which are often present subperiosteally, multinucleated giant cells and considerable extravasated blood may appear. The cellular elements within such foci can be quite varied.

On histologic examination, osteoclasts are to be found in abundance during all active stages of the evolution of the pathologic process. During the resorption of the original bone, they are to be found on the surfaces of the enlarged haversian canals and the surfaces of the trabeculae, both periosteally and subperiosteally. They are, of course, found in association with Howship's lacunae. As the original bone is being replaced, the new bone appears in the connective tissue; the removal and the rebuilding of this new bone are also associated with numerous osteoclasts. In our experimental work, we found that the emphasis which the older pathologists laid on osteoclasts as a special feature of the pathologic picture of generalized osteitis fibrosa cystica was justified. In the experimental condition, the appearance of great numbers of osteoclasts is a particular feature in relation to the decalcification and resorption of the original bone and of the newly formed connective tissue bone.

It is striking that in this disease the tendency to resorption and decalcification by far exceeds the tendency to new bone formation. This is explained by the constant drain on the calcium reserves to which a patient or animal suffering from chronic hyperparathyroidism is subjected. The predominance of the process of resorption over new bone formation is one of the features of Recklinghausen's disease which distinguish its microscopic picture from that of Paget's disease. As previously indicated, the appearance of osteosclerosis in rats on an adequate calcium diet, given injections of parathyroid extract over a long period, is evidence of healing in association with continued resorption.

While it is true that areas of a bone with Paget's disease may present a histologic appearance indistinguishable from that of Recklinghausen's disease, in most areas of Paget's disease new bone formation outruns resorption. Thus, there is little reason for confusion between them. The newly formed bone of Paget's disease takes on a distinguishing microscopic picture, owing to the numerous thick, irregular and dark-staining cement lines, which give the bone the appearance of an irregular mosaic—a feature to which others have alluded, but to which Schmorl [5] ascribed diagnostic significance.

In Recklinghausen's disease, such an irregular mosaic architecture is rarely to be observed except possibly in the skull, if it is thickened. When, in certain regions, deposition of new bone can be maintained in excess of resorption, cement lines appear, but these are never as irregular, as numerous or as thick as those in Paget's disease. Thus, the irregular mosaic-like appearance, so prominent in the microscopic picture of Paget's disease, is not created in Recklinghausen's disease.

In chronic experimental hyperparathyroidism we did not find the irregular mosaic structure. In the bones of young guinea-pigs receiving intermittent injections of parathyroid extract-Collip a large number of new cement lines resulted. These were, however, fairly regularly disposed. They were indicative of the periodic decalcifications and restorations to which these bones were subjected during the long course of intermittent chronic hyperparathyroidism.[30d]

Although new bone formation is not excessive, it may be observed in both clinical and experimental hyperparathyroidism. Even while original cortical bone is being resorbed and the canals of its blood vessels are being widened, a low power survey of such a cortex will show the deposition of narrow margins of newly formed bone covered by osteoblasts on the walls of the enlarged canals. These osteoid margins are in no way comparable to the thick osteoid borders observed in osteomalacia and in rickets. It is one of the peculiarities of bone as a tissue that, in spite of the existence of conditions causing its resorption and depletion, a tendency exists to counteract the resorptive forces by new bone formation.

The advanced stages of Recklinghausen's disease are frequently associated with brown lesions of the bones, composed of giant cell masses. These are generally designated as giant cell tumor areas. However, a bone may become extensively diseased without the appearance of such giant cell tumors, even microscopically. When present, their number and size vary greatly in different cases. Some are minute, whereas others are large enough to expand part or all of the circumference of a long tubular bone. The largest have been known to reach the size of a child's head. If revealed only on microscopic examination, they appear as nests of giant cells in a cellular, fine-fibered marrow, which also contains numerous granules of blood pigment (microscopic

brown tumors). They are most likely to be present in the metaphyses, and fractures frequently occur at their sites if they reach a large size. Their presence in any region of a bone denotes marked progress of the pathologic process.

Histologically, these brown giant cell masses are composed of a spindle cell connective tissue stroma which seems to be continuous with the ordinary outlying connective tissue stroma. The giant cells, which may be so numerous as to overshadow the supporting stroma completely, are identical with the osteoclasts; they have phagocytic activities and often contain changed red corpuscles or hemosiderin. Frequently the number of giant cells is relatively small. The brown color of these tumors is apparently dependent on hemorrhage, the color being the result of blood pigment within phagocytes in the fibrous connective tissue.

Healing processes may be observed in brown tumors; they take place through conversion of the affected area into a cell-poor, sclerotic connective tissue, which may even become partly calcified. Collections of giant cells under such circumstances may remain in the peripheral zones. It is possible that these lesions may even disappear spontaneously. Large giant cell areas may eventually become cystic, with little of the original tissue remaining; cyst formation is also considered as evidence of spontaneous healing. In cases of Recklinghausen's disease in which parathyroid adenomas were removed, giant cell areas observed roentgenologically have been reported as disappearing.

The mode of origin and the significance of the giant cell masses have been debated since von Recklinghausen's time. One question seems definitely settled: that is, they are not genuine tumors or blastomas. Whether they are to be considered as a special type of inflammatory or reactive new bone formation, in consequence of hemorrhage that has occurred in fibrosed marrow, cannot be decided now. This view, however, seems to be the most acceptable one at present.

There has been active discussion as to whether the periosteal and the central epulides of the jaw (which may occur without hyperparathyroidism) are to be differentiated pathogenically from the brown tumor masses of Recklinghausen's disease.[44] It seems fair to assume that since the epulides and the solitary giant cell tumors (which occur especially in the epiphyses) frequently have the characteristics of blastomas, they are to be separated from the brown tumors of Recklinghausen's disease, which resemble them only histologically. Pick,[45] among others, recently expressed himself in favor of this point of view.

There is also considerable variability among the cysts. They may be quite numerous; they may be absent entirely; sometimes they are

44. Hellner, H.: Arch. f. klin. Chir. **165**:229, 1931.

45. Pick, L.: Verhandl. d. Gesellsch. f. Verdauungs- u. Stoffwechselkr. X. Tag. Budapest, 1930, Leipzig, G. Thieme, 1931, p. 146.

recognized only microscopically. When they are present and recognizable grossly, the involved bone may contain but few, or it may show them in such multiplicity as to give the appearance of generalized cystic degeneration. The cysts occur most frequently in the larger areas of fibrous marrow and are located within the metaphyses or diaphysis. They may expand the shaft of a bone and be the underlying cause of fracture. At other times, cysts may extend to the periosteum, being separated from it by a thin fibrous layer of tissue and a shell of bone.

The larger cysts are unilocular or multilocular. When they are multilocular, the dividing septums are fibrous tissue walls within which

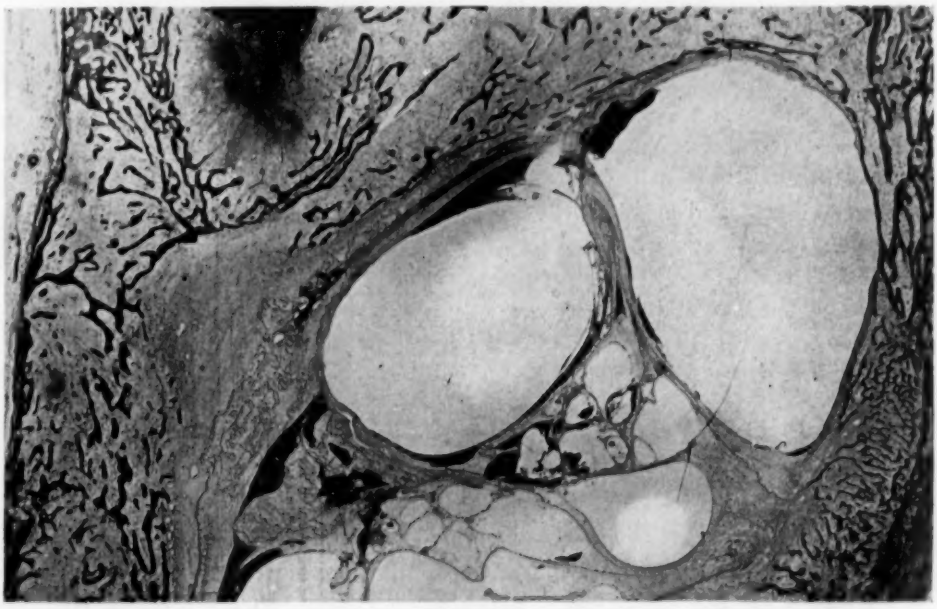

Fig. 4.—A long tubular bone showing cysts and a giant cell tumor area; the brown lesion is observed in the upper left portion of the photomicrograph; several large cysts and a number of smaller cysts are also observed; newly formed bone is seen about the cysts on the left; × 4.

thin trabeculae of bone may be found. These larger cysts may be lined by a condensed layer of fibrous tissue, beneath which newly formed bone may be present; in others the wall is less well defined. Coagula of thin albuminous material can often be found in the larger cysts; such coagula may be admixed with red blood cells, phagocytic cells and sometimes cholesterol crystals. Some of the cysts contain large amounts of blood and fibrinous clots, while others may be empty. The intercystic tissue is frequently fibrous tissue, with or without hemorrhage, and new bone in various stages of formation is also observed between the cysts (fig. 4).

There has been much conjecture concerning the possible modes of origin of cysts, particularly of the larger ones. It seems fair to assume that they may arise in several ways. Some of them certainly have had their beginning as a result of edema and degeneration of the fibrous marrow, as microscopic examination reveals spaces in the meshes of the edematous fibrous tissue. These spaces may enlarge and fuse, the intervening septums undergoing degeneration, with the formation of larger cysts. Hemorrhage, through the rupture of vessels, may be a contributory factor in altering their appearance and content. Cysts may also result from degenerations occurring within giant cell tumor areas; large cystic spaces filled with thin, blood-stained fluid appear as a result. In addition to the larger cysts, the connective tissue (in the porous cortex and between the newly formed trabeculae of bone in the fibrous marrow) contains a great abundance of small dilated, cystlike blood and lymph channels. These dilated spaces arise through stasis. Cysts of this type were seen in our animals suffering from chronic hyperparathyroidism.

A long tubular bone showing the advanced pathologic changes of generalized osteitis fibrosa cystica may show evidences of recent or healed fractures. Such bones break with the slightest trauma and frequently such a fracture may be the first serious clinical feature to draw attention to the disease. Fractures are much more common in Recklinghausen's disease than in Paget's disease. The resultant deformities may be worse even than those observed in osteomalacia. It is surprising that in spite of the sluggishness of the periosteum in proliferating, fractures heal fairly readily, although refractures may occur.

Advanced Pathologic Changes in Other Bones.—The foregoing description of the pathologic changes in a long tubular bone much involved by the disease may apply to any long tubular bone in the body. Essentially the same pathologic changes are present in any other bone markedly involved.

The vertebral column may be deformed, showing kyphosis or scoliosis or both. In advanced cases, a really continuous subperiosteal bone layer may be absent. Owing to the marked decalcification of the bodies, the turgid intervertebral disks become expanded and discoid, with resultant reduction in the superior-inferior diameter, especially through the center of many bodies. Thus, the fishlike spine appears. (Such appearances are manifested in other conditions also, especially in senile osteoporosis.) Beneath the expanded intervertebral disks there is usually a considerable layer of newly formed trabeculae of finely condensed bone. Between these trabeculae there is a vast increase of fibrous tissue, and numerous osteoclasts are to be observed on the sur-

faces of such trabeculae. Within the deeper substance of the body, a great amount of atrophy of the original trabeculae occurs; there is likewise a great amount of marrow hemorrhage; there may be cystic spaces and giant cell tumors. The normal lymphoid marrow may also persist if the fibrous transformation is not too extensive (fig. 5).

The deformity of the vertebral column, together with the changes in the ribs and sternum, may result in a badly misshapen thoracic cage. The ribs can become extremely atrophic, and some, especially the lower ones, may assume irregular shapes and impinge on the iliac crests.

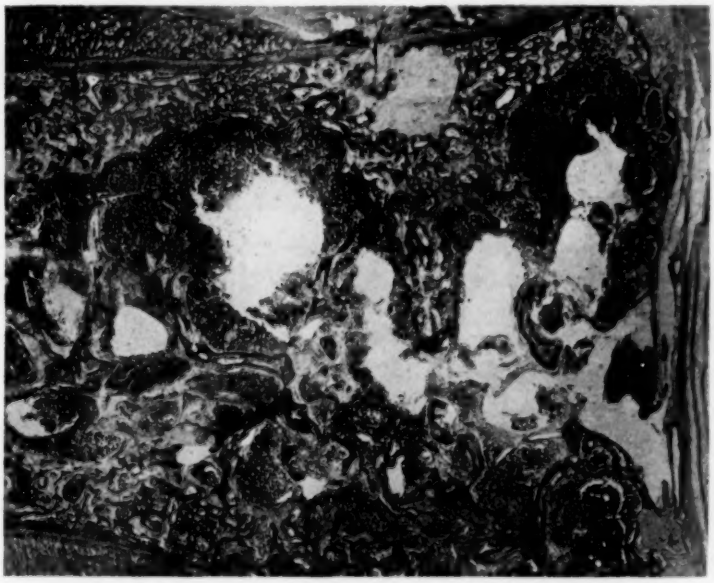

Fig. 5.—A longitudinal section of a vertebral body is shown; beneath the intervertebral disk, considerable newly formed trabeculae of finely condensed bone are seen; the other trabeculae are atrophic, and marrow hemorrhage is present; cortical defect of the body is observed on the right; × 4.

Calluses at the sites of healed fractures are frequently observed, while the ribs may show cortical expansion owing to the presence of cysts and giant cell tumors.

Deformity of the pelvic bones also results. The brim becomes extremely asymmetrical and distorted and much reduced in size. The distortion in the shape of the pelvis may approximate the type of deformity observed in advanced cases of puerperal osteomalacia. This is one of the reasons why advanced generalized osteitis fibrosa cystica has been confused with osteomalacia. The iliac bones are likely to become

expanded; when they are replaced by pathologic new bone, they are easily compressible and flexible.

The short tubular bones may show pronounced changes with cysts and giant cell tumors, though they are less likely to present as marked degrees of implication as long tubular bones. The tarsal and carpal bones may be atrophic, with no other involvement.

The bones of the calvarium may be thin, atrophic and quite pliable; the thinning may proceed to such degree that bony defects are present. On the other hand, but not as often, the calvarium may be thickened, in many ways, especially roentgenologically, suggesting the appearance of the skull in Paget's disease. Thickening of the skull in certain cases of generalized osteitis fibrosa cystica was one of the reasons why this disease and Paget's disease were closely linked as different manifestations of a common basic disturbance. This theory, in view of the present knowledge of hyperparathyroidism, is now definitely discredited. Why the skull thickens in certain cases of Recklinghausen's disease is not known.

The thinned calvarium, from which the pericranium is stripped, presents a rough, vascular-looking surface; the sutures are obliterated; the calvarium may easily be cut with a knife. The cut surface shows disappearance of the normal division into inner and outer tables with intervening diploe. The bone that has replaced the normal components is made up of intertwining new-formed trabeculae. They have a more or less parallel arrangement immediately under a poorly cellular periosteum. The outer trabeculae are coarse-fibered and contain calcium; deeper, the trabeculae are irregular and show less calcium on staining. The same relationship holds from the dural surface outward. The intertrabecular spaces are filled with connective tissue, and this tissue becomes more or less continuous with the periosteum on the outer surface and the dura on the inner surface. Osteoclasts are seen in large numbers on the surface of original bone and also on the new bone that is being transformed. In some areas large fibrous foci without any new-formed bony trabeculae are to be observed, within which some scattered osteoclasts may be found.

A calvarium that is thickened is usually not uniform in this change. The region most thickened may measure as much as 2 cm. or even more. The cut surface in such an area is finely porous and usually injected. The sutures, as in the thin calvarium, are obliterated, and the vascular grooves may be quite deep. The histologic appearance of a thickened zone is that of complete replacement of the normal architecture by slender trabeculae which are most regularly arranged externally and internally; the trabeculae between the inner and outer layers are irregular in shape and form a close-meshed spongiosa. The marrow is fibrous

throughout. The cement lines may be fairly numerous, but they never reach, either in number or in irregularity, the proportions they do in Paget's disease.

Progressive Atrophy of Bone: Early Stage of the Disease.—In the early stages of the evolution of Recklinghausen's disease, the pathologic picture of the skeleton is in every way comparable to the pathologic picture of the condition described by Askanazy [10] in 1901 as "progressive bone atrophy." [46] Askanazy,[47] in 1932, discussing progressive atrophy of bone, attempted to establish for it a distinct and separate place in the pathology of bone. He would not definitely admit that progressive atrophy is an early stage of generalized osteitis fibrosa cystica, holding that the distinguishing feature of the microscopic picture in this condition is the absence of new bone formation. A case of Recklinghausen's disease described by Bergstrand,[38] in which there were only very mild changes in the bones disputes this point of view. Two prune-sized parathyroid adenomas were found at autopsy. The bones showed active resorption, but there was no evidence of new bone formation.

There can be no doubt that the histologic picture of progressive atrophy of bone appears under a number of circumstances, in man and in animals. From these examples the inference may be made that the pathologic picture of progressive atrophy of bone is not one that is specifically related to any single etiologic factor. In this connection, Schmorl [48] stated that the pathologic changes of progressive atrophy of bone with its dissecting resorption may without any question be observed in Recklinghausen's disease. In four cases showing progressive atrophy of bone he found parathyroid tumors, and in three of these, multiple giant cell tumors were also present; metastatic calcification was not observed in any of them. In all four cases Schmorl described dissecting

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46. His patient, a woman 54 years of age, died of suppurative peritonitis following rupture of the pelvis of a kidney by a renal stone. At autopsy he found metastatic calcification of the stomach, lung and kidneys. Gross examination of the spine and sacrum gave him the impression of a mild osteoporosis; microscopically, he found in all sections that the bony trabeculae were markedly resorbed, and from 40 to 80 osteoclasts were present in each field. The bony trabeculae were pierced through by newly formed connective tissue tracts, while, on the whole, the intertrabecular marrow was not fibrosed. This peculiar dissection of the trabeculae has come to be called, in the pathology of bone, "dissecting resorption." The surfaces of the original trabeculae also showed increased connective tissue and osteoclasts. Bony deformity was not present. In the mediastinum there was a necrotic calcified tumor mass which Askanazy designated as a thyroid carcinoma, difficult to differentiate microscopically from a parastruma. He speculated on the relation of this tumor to the bone lesion.

47. Askanazy, M.: Schweiz. med. Jahrb., Basel, B. Schwarz & Co., 1932, p. CVII.

48. Schmorl, G.: Verhandl. d. deutsch. path. Gesellsch. **21**:71, 1926.

resorption in the spongiosa of the vertebrae. Dissecting resorption is characterized microscopically by the perforation or dissection of original bony trabeculae by tracts of connective tissue (fig. 6). Furthermore, such trabeculae also show resorption on their surfaces. If new bone is deposited on the surfaces of trabeculae undergoing dissecting resorption, it is never profuse; such depositions are arranged in parallel formation. Dissecting resorption is not observed in Paget's diesase.

In chronic experimental hyperparathyroidism in guinea-pigs, Bodansky, Blair and I [30c] found that the lesions in the bones corresponded more with those of progressive atrophy of bone (as described by Askanazy in man and by Lévy [49] and Pick [50] in rodents) than with those more regularly found in Recklinghausen's disease. Lévy described an adult tuberculous rabbit in which metastatic calcification of the soft

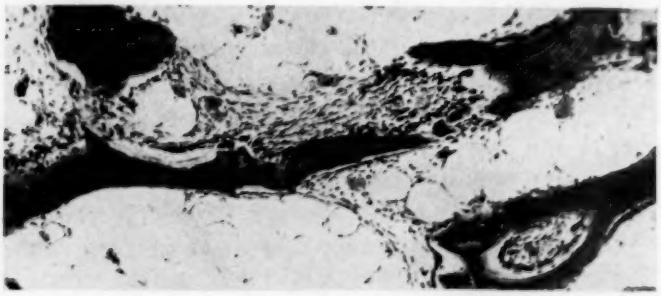

Fig. 6.—Dissecting resorption of trabeculae at the (epiphyseal) end of a long tubular bone; there is dissection or perforation of the original trabeculae by tracts of connective tissue; × 125.

tissues was discovered at autopsy. Grossly, the bones appeared normal in form and structure; microscopically, generalized fibrosis was discovered, which was most marked in the tibia. Lévy did not designate by name the condition that he described, but Christeller,[51] who restudied material in this case, was inclined to consider it one of acute progressive atrophy. He based his opinion on the fact that osteoblasts and osteoid tissue were practically absent in the greatly fibrosed bone. Pick described a hedgehog the skeleton of which showed nothing unusual grossly. On microscopic examination, the bones presented terrific lacunar resorption by osteoclasts, and both the compact and the spongy bone were vascularized; the enlarged canals of the blood vessels con-

49. Lévy, E.: Arb. a. d. Geb. d. path. Anat. Inst. Tübingen **6**:555, 1908 (pt. 2).
50. Pick, L.: Berl. klin. Wchnschr. **54**:797, 1917.
51. Christeller, E.: Ergebn. d. allg. Path. u. path. Anat. **20**:1, 1923 (pt. 2).

tained connective tissue. Fibrosis of the marrow was also present. The soft tissues showed metastatic calcification. In neither Lévy's nor Pick's animals was there any abnormality of the parathyroid glands. In rodents, progressive resorption of bones is not attended by any considerable new bone formation, so that the pathologic picture strikingly resembles that of progressive atrophy of the bone in man, no matter what the cause of the resorption.

Resorption of Bone: Its Rôle in Hyperparathyroidism.—In discussing the pathologic changes occurring in hyperparathyroidism, it was repeatedly stressed that these are brought about by progressive resorption of the original bone and replacement of it by connective tissue in which newly formed bony trabeculae appear. The newly formed trabeculae are themselves greatly subjected to resorption. Associated with the resorption is the presence of large numbers of osteoclasts in Howship's lacunae, both on the surfaces of the original bone in the process of resorption and on the surfaces of the newly formed trabeculae. Osteoclasts are present in great numbers during the active stages of the evolution of the disease. In fact, osteoclasts are more numerous in this disease than in any of the generalized malacic diseases, including even Paget's disease.

In spite of the fact that the last twenty-five years have brought to light a vast amount of new physiologic and chemical knowledge concerning many diseases—such as rickets, osteomalacia and hyperparathyroidism—some of the tenets regarding resorption laid down by histologists and cellular pathologists before these advances are still generally accepted unquestioningly as applicable without variation to every type of disease of bone. The voluminous literature on the question of bone resorption in general is so dominated by dogmatic exposition that unless one proceeds with the utmost caution in considering bone resorption in any particular disease affecting the skeleton, there are always ready pitfalls. The avoidance of these is dependent on the intelligent application of present physiologic knowledge to the interpretation of the pathologic picture.

It is plain that views concerning resorption of bone must be interpreted with due regard to the nature of the material under investigation. Thus the resorption brought about by the ingestion of acids or acid salts will differ in several ways from that due to starvation. Furthermore, Bodansky, Chandler and I [52] demonstrated that the resorptive picture following the ingestion of an acid salt like ammonium chloride is dependent on the age of the animal, and is modified by the amount of bone-forming minerals ingested daily. In any event, the

52. Jaffe, H. L.; Bodansky, A., and Chandler, J. P.: J. Exper. Med. **56**:823, 1932.

resorptive picture in these conditions differs from that in acute inflammatory disease. The pathologic resorption of bone (that is, the resorption of bone except under physiologic conditions) has been studied for a very long time; more than one hundred years ago it was the subject of intensive investigations. These studies have brought to light that pathologic resorption proceeds with varying intensities, with even markedly different histologic pictures in different conditions. The innumerable investigations on resorption of bone have centered about the osteoclast (its origin and function), the phenomena appearing in the ground substance (including the question of preliminary decalcification) and the rôle of the vascular system (inclusive of the formation of new vessel canals in pathologic resorption—genuine Volkmann canals). More intensive consideration and evaluation of these factors will follow.

Osteoclastic Activity: Osteoclasts dominate the histologic picture in Recklinghausen's disease. Since I am opposed to the view that the osteoclast is directly responsible for the initiation of the resorption in this disease (for that matter, in any disease of bone), it is fitting here to consider the particular function of the osteoclast in the whole mechanism of the resorptive process. Pommer's views will be given in detail because of their tremendous influence on reasoning relative to resorption of bone. After von Kölliker's [53] recognition of the multinucleated giant cell, which he called "ostoclast" (bone breaker), in physiologic resorption, Pommer became the outstanding protagonist of its importance in pathologic processes. Beginning in 1881 he so strongly fought for the conception that the osteoclast is capable of directly eroding and removing bone without its preliminary decalcification that this view became a resorption saga in the pathology of bone. The tremendous support that accrued to Pommer's view was partly accounted for by the fact that cellular pathology was then in complete domination of conceptions in pathology. His view thereby carried tremendous influence with his contemporaries, especially with the younger pathologists being trained at that time.

In 1881, Pommer [54] declared himself to the effect that an intensive examination of his own material obliged him to support Kölliker in the view that Howship's lacunae arise through resorption by osteoclasts; he further declared that the borders of Howship's lacunae show no evidence of decalcification—thus supporting von Kölliker's view that Howship's lacunae are, without exception, delineated by normal bone

53. von Kölliker, A.: Die normale Resorption des Knochengewebes, Leipzig, F. C. W. Vogel, 1873.

54. Pommer, G.: Sitzungsb. d. k. Akad. d. Wissensch. Math.-naturw. Cl., Wien **83-84**:17, 1881.

tissue. In 1883, he[55] again discussed this subject, stressing the view that the ground substance and bone cells are entirely passive in lacunar resorption, as in all other changes; that Howship's lacunae arise only through the activity of osteoclasts, the shapes of which conform with the adjacent Howship's lacunae, and that the osteoclasts resorb the bone by assimilating the organic ground substance and mineral salts simultaneously. In 1885, in his well known monograph on osteomalacia and rickets,[56] he pursued the same path of reasoning regarding resorption that he had previously held, only he found it necessary to expand the subject so as to discuss the rôle of the perforating canals, as well as to include—under the general theory of osteoclastic resorption—an explanation of how the osteoclasts play their part in the pathogenesis of senile atrophy, atrophy due to inactivity and the various other types of local atrophy.

He did not swerve from his original thesis: that in all types of resorption the osteoclast is the original, direct, resorbing cell; that there is never any preliminary decalcification of bone that is in the process of being resorbed, and that the bone ground substance, bone cells and processes are entirely passive. All types of atrophy he therefore conceived as arising from deficient deposition of new bone following mild degrees of osteoclastic lacunar resorption; he stated that the evidences of existing or previous lacunar resorption may be very slight and are limited to the subperiosteal region; he therefore found it necessary to reject the conception that thinning of bone in the various local atrophies results from "smooth resorption," a view that had gained considerable support and which conceived the atrophy as having arisen without osteoclastic lacunar resorption. Pommer's view of atrophy was based on the well known physiologic principle concerning growth of bone—that resorption and apposition go on throughout life—and he averred that when the deposition does not compensate for resorption, atrophy ensues.

By 1925 he arrived at the conclusion that no matter what the basis for an osteoporosis is, the process is the result of osteoclastic resorption on the foundation of a hyperemia of marrow vessels. This is greater, the more acute the process; added to this, there is the fact that new apposition does not compensate for resorption.[57] Thus, Pommer's juggling of the definition of the osteoclast, during forty years, gave to the meaning of osteoclast a variable significance. In addition to recognizing the classic type of osteoclast, he averred, particularly more

55. Pommer, G.: Virchows Arch. f. path. Anat. **92**:296 and 449, 1883.

56. Pommer, G.: Untersuchungen über Osteomalacie und Rachitis, Leipzig, F. C. W. Vogel, 1885.

57. Pommer, G.: Arch. f. klin. Chir. **136**:1, 1925.

recently, that small cells, with even one nucleus, seen in bone undergoing resorption may also be of the nature of osteoclasts.[58]

Regarding the function of osteoclasts in resorption, it is my opinion that they must be considered aggressive, reactive, phagocytic cells which arise locally. I am not convinced that they themselves exert a dissolving influence on the bone before they remove the ground substance. On the basis of available knowledge it seems that it would be better to consider osteoclasts as bone resorbers rather than dissolvers; I should agree with Arey,[59] who takes issue with the use of "osteolytic" as a term interchangeable with "phagocytic." More accurately speaking, osteolysis by osteoclasts implies the direct dissolution of unchanged bone by these cells; phagocytosis of the bone implies the removal of changed bone. Whether osteoclasts produce osteolysis or phagocytosis of bone depends on whether the osteoclasts dissolve the inorganic salts before they remove the organic matrix. Our histologic studies of the bones of animals subjected to experimental hyperparathyroidism (especially acute) demonstrated that decalcification of bone (along the margins of the haversian canals and under the periosteum and endosteum) occurs before the decalcified matrix is removed by phagocytes. In acute hyperparathyroidism, phagocytosis may be carried on by polymorphonuclear leukocytes in addition to osteoclasts. I believe that both in chronic experimental hyperparathyroidism and in clinical hyperparathyroidism osteoclastic activity is predicated on preliminary decalcification

58. Although his views were not wholly original, they crystallized the theories of osteoclastic resorption held by many of his contemporaries. At the same time they utterly rejected a great many views held by others. A number of these had validity, but were denied acceptance by the sheer force of the repeated arguments piled up against them by Pommer. For instance, he rejected the theory of participation of the bone cells and processes, though it must be apparent to every one who has carefully studied bone in the process of resorption that the bone cells in the vicinity of the resorptive area undergo extensive changes; he held that the ground substance is entirely passive during the process of removal and shows no preresorptive changes, although any one studying ground-disk preparations of osteomyelitic or other pathologic bone will find that the enlargement of the vessel canals is accompanied by changes in the ground substance, which, in the region of the resorption, appears as large, irregular, coarse granules (Jaffe, H. L.: Arch. Surg. **20**:355, 1930); he consistently refused to acknowledge that preliminary decalcification of the ground substance is possible, and he held that the osteoclasts are solely responsible for removal of the calcified bone, although he never offered any evidence that this is so, except that there is a positional relationship between the osteoclasts and Howship's lacunae; he repeatedly denied the possibility in vascular resorption (when blood vessels and granulation tissue invade the haversian canals and marrow spaces) that the resorption occurs in any mode except through the endothelium of the blood vessels acting as osteoclasts. The details concerning such changes will be considered with phenomena appearing in the ground substance during resorption.

59. Arey, L. B.: Am. J. Anat. **26**:316, 1920.

of the ground substance. This explanation will be amplified in the succeeding pages.

Phenomena Appearing in the Ground Substance: Contrary to the point of view of Pommer and his adherents—that the ground substance, bone cells and processes are entirely passive during the resorptive process—were the beliefs of a number of other observers. Their views found the strongest protagonist in von Recklinghausen, who devoted a good portion of his important monograph on rickets and osteomalacia, published in 1910, to the exposition of the opposite point of view.[60] His treatise was the lifetime's labor of a careful investigator. His conclusions were based on the microscopic examination of undecalcified fragments of bone fixed in Kaiserling's solution or in formaldehyde solution and stained with aqueous thionine, a modification of the original method of Schmorl. There are several unfortunate features about this monograph which have led to both misinterpretation of his point of view and neglect of it. Von Recklinghausen discussed resorption of bone in general, but because he had to a great degree used rachitic and osteomalacic material the impression has been created that he conceived the true osteoid borders in these conditions to be the result of decalcification —a point which careful reading of the monograph disproves, and which was evidently far removed from his own view.

On the nature of the apparently calcium-free zones bordering calcium-bearing bone, much can be said, as observations concerning the time and the means by which calcium is deposited during the formation of bone are certainly not incontrovertible. Pommer has consistently upheld the view that every calcium-free zone (osteoid zone) bordering fully mature bone must be considered as a zone of bone which, in the process of its formation, has not as yet become calcified. In other words, it is an uncalcified zone and not one resulting from decalcification. The delimiting border between the calcium-free osteoid zone and the calcium-containing bone is a transition zone of calcified granules or a cement line (which is sharp, buckled, toothed or straight).[61]

Pommer's well known method for demonstrating these osteoid borders by the use of Müller's fluid for partial decalcification, followed

60. von Recklinghausen, F.: Untersuchungen über Rachitis und Osteomalacie, Jena, Gustav Fischer, 1910.

61. However, Weidenreich (Ztschr. f. Anat. u. Entwcklngsgesch. **69**:382, 1923) stirred up much controversy (Pommer: Ztschr. f. Anat. u. Entwcklngsgesch. **75**:382, 1925) when he stated that the osteoid borders may be nothing but artefacts, and that such borders are not to be found in ground-disk preparations; from this extreme view Weidenreich has apparently retreated, as in his contribution to the von Möllendorff handbook of histology he gives a more traditional discussion of these osteoid borders (von Möllendorff: Handbuch der mikroskopisches Anatomie des Menschen, Berlin, Julius Springer, vol. 2, pt. 2, p. 391).

by staining with basic dyes, has been applied with many other methods that demonstrate their presence. I am not fully convinced that the difference in staining between the so-called calcium-containing and calcium-free bone in osteomalacia by the Pommer method is due to the absolute lack of calcium in the latter and its presence in the former. I am inclined to believe that it may be dependent on the nature of the protein of the ground substance. By this, I do not wish to deny that quantitatively there is an absolute difference in the calcium content between them; rather, I wish to affirm that the staining differences may be influenced by other content.

Nor can I agree with Ribbert [62] that these differently staining zones are wholly dependent on decalcification for their origin. Using carmine, which stains the apparently calcium-free zones red, he became more or less the founder of the school that believes that there is a preliminary decalcification in all resorption of bone. However, he and those of his followers who supported him in the view that osteoid borders in all diseases of bone are the result of decalcification were undoubtedly incorrect, for in rickets and osteomalacia there is no question but that these osteoid borders are the result of deficient calcification of bone in the process of formation. Von Recklinghausen, who was in a sense a follower of Ribbert, makes plain his own distinction on this point, declaring that the designation "osteoid" should be referable only to bone that is calcium-poor or calcium-free, but at the same time he implies that such bone is in the process of progression toward calcification. Thus, he would, unlike Ribbert, exclude all borders of bone that are the result of regression or decalcification from classification as osteoid. This concurs entirely with my own view. It should therefore be apparent that no criticism of von Recklinghausen's conception of resorption of bone can be directed against him on the ground that he considered genuine osteoid borders as zones of decalcification.

However, in von Recklinghausen's description of the mechanism of resorption of bone, he introduced a large number of complicated terms which confuse and involve the explanations. Because it is important to understand clearly his use of these terms, they are summarized here. In describing the changes occurring in the bone cells and processes during resorption, he indicated that the first step in the course of their final destruction was a knobby swelling of the processes and also a swelling of the bone-cell, which he called *Onkose*. He recognized, however, that bone cells and processes may disappear without *Onkose*. In rickets *Onkose* was most considerable at the border between the original bone and the osteoid zone, while in osteomalacia it was not very abundant. About cells and processes in the *Onkose* stage he described softening of

62. Ribbert, H.: Virchows Arch. f. path. Anat. **80**:436, 1880.

the firm portion of the ground substance, and he designated the area of softening as a cell territory; he conceived this in much the same sense in which Virchow [63] conceived a cell territory. Territories of softened ground substance about Volkmann canals or in osteoid tissue he described as perivascular or coatlike territories.

In his consideration of the production of such territories, von Recklinghausen recognizes "thrypsis," which he defines as a slow liquefaction of the various components of the ground substance; softening sets in, which, when the cement or ground material disappears, permits such elements as the collagenous fibrils, the bone cell capsules and the sheaths of the processes to become very prominent. During this process of dissolution and softening, the various components of the ground material appear as fragments or granules; afterward, there is complete disappearance of the ground substance, owing to shrinkage and liquefaction. Von Recklinghausen made this distinction between thrypsis and halisteresis: Thrypsis defines the inclusive process of dissolution of the ground substance of bone (whether or not the bone is calcified), while halisteresis is a part of the all-inclusive process of thrypsis which specifically relates to the solution of the calcific or mineral elements of the ground substance.

One of the points in the von Recklinghausen concept on which there has been much controversy is the interpretation of the *Gitterfiguren* (lattice-figures), which, according to him, are the consequences of softening of bone tissue, whether osteoid or completely calcified. He conceived these figures to be the result of thrypsis. He demonstrated their presence by filling with gas the lattice spaces that result in ground substance undergoing thryptic liquefaction. Thus, *Onkose*, cell territories and the lattice-figures were regarded as evidence that thrypsis was taking place.

He held that if microscopic evidences of thrypsis are observed in bone that contains calcium, it is necessary to conceive that at the onset of the thryptic disintegration the mineral portions had to be dissolved out. This he considered as an indirect proof of the occurrence of halisteresis. Finally, von Recklinghausen stated that he could not give positive information concerning the celerity with which disintegration of the ground substance occurred. In considering the entire process of thrypsis in rickets and osteomalacia, he tried to show that whenever it was present the bone involved had to be considered as bone in the course of destruction. Such appearances could be seen on the surfaces of mature bone undergoing decalcification. Furthermore, thrypsis could also be observed in genuine osteoid tissue. When genuine osteoid tissue shows evidences of thrypsis, it is undergoing dissolution. Von Recklinghausen

63. Virchow, R.: Die Cellularpathologie, Berlin, A. Hirschwald, 1871, vol. 1.

also indicated that very slight signs of thrypsis may, on careful examination, be observed in normal bone during the process of growth. In regard to rickets and osteomalacia, he made the significant comment that much of the genuine osteoid tissue that is formed in these diseases never goes on to calcification, even though the lesion may heal; much of this osteoid tissue has to be removed. He had observed, as many others had, that osteoclasts do not play a significant rôle in the resorption of rickets and osteomalacia.

This brings one directly to the problem of the occurrence of thrypsis and halisteresis in hyperparathyroidism. In our [64] experimental studies of hyperparathyroidism, the mechanism by which the original and newly formed bone is removed had always been of particular interest to us. It is well known that parathyroid extract-Collip produces a disturbance in the acid-base equilibrium, and its injection leads to an increased excretion of the mineral salts, especially calcium and phosphorus, particularly through the urine. This histologic study of a great number of fixed and decalcified bone sections (as well as ground-disk preparations) from animals suffering from experimental hyperparathyroidism has led us [64] to the conclusion that hyperparathyroidism (as a result of the changes that it induces in the tissue fluids circulating about the bone) has but one primary effect on the bone: the solution of mineral salts out of the bone, at the surfaces of contact between the tissue fluid and the bone. The immediate effect of hyperparathyroidism is the disappearance of osteoblasts from the surfaces of the normal bone, where bone formation is normally in progress. This is most apparent where new bone formation is most active. From our observations we have been led to conclude that all other appearances and effects are secondary to the cessation of new bone formation and the associated production of minute and narrow zones of decalcification on the subperiosteal, subendosteal, trabecular and haversian canal surface. Even in an animal like the rat, in which osteosclerosis may eventually develop, resorption continues throughout the course of treatment with parathyroid.

We have been able to convince ourselves that thrypsis and halisteresis are at the basis of this primary decalcification, as in favorable specimens (especially when severe, acute hyperparathyroidism had existed) swelling of the bone cell lacunae and disintegration of their nuclei were observed in narrow decalcified zones; this occurred even in the absence of osteoclasts. Furthermore, ground-disk preparations invariably showed that the ground substance in these narrow zones contained large granules. Occasionally, we have observed, especially in acute hyperparathyroidism, that polymorphonuclear leukocytes had begun actively to phagocytose the decalcified organic matrix, sometimes

64. Jaffe and Bodansky.[30a] Jaffe, Bodansky and Blair.[30c] Jaffe, Bodansky and Blair.[30e] Jaffe, Bodansky and Blair.[42]

even in the absence of osteoclasts. Osteoclasts could be seen forming from the marrow connective tissue adjacent to the decalcified bone margins, and these osteoclasts rapidly proceeded to phagocytose the decalcified organic matrix, with the production of deep lacunae of Howship.

As the chronic hyperparathyroidism proceeded, especially in as susceptible an animal as the dog, the number of osteoclasts became quite numerous. Both in clinical and in experimental hyperparathyroidism, great numbers of osteoclasts appear, because both the original bone and any newly formed bone that may appear in the connective tissue are constantly subject to drastic decalcification, and the osteoclasts arise to carry on the phagocytosis of the decalcified matrix.

Abnormal Vascularization: Changes in the Canals of Blood Vessels: In Recklinghausen's disease, the resorption of the bone is accompanied by enlargement of the existing canals of blood vessels. Abnormal numbers of perforating canals, in the sense in which Volkmann [65] described them in inflammatory diseases, do not appear. Regarding the perforating canals, Pommer also correlated their origin with the theory of osteoclastic resorption, stating that such canals are channels prepared for blood vessels and that they arise in mature bone tissue through the resorbing activity of the vessel sprouts. In their incipient stages, these sprouts are conceived by him as solid protoplasmic masses that function as osteoclasts in the process of resorption. They produce a passage for a blood vessel; finally the vessel arises through a space developing in the protoplasmic mass. The protoplasmic mass may be aided in the resorption of the formed bone by osteoclasts. Pommer made a distinction between true and false perforating canals, based on histologic appearances; he held that a true perforating canal has a pointed protoplasmic mass at its head, and that it is not surrounded by any accompanying lamellae; he further stated that only the true perforating canals could be considered as resorption canals, newly formed in mature bone.

The large and exhaustive literature that exists concerning the nature, the mode of origin and the histologic appearances of these canals is sufficient to tax the patience of any investigator, let alone the vast amount of print that is devoted solely to polemics. The controversy that has more recently developed between Zawisch-Ossenitz [66] (who was supported by her teacher, Schaffer) and Pommer [67] concerning the perforating canals has again opened the subject. On the basis of her studies, Zawisch-Ossenitz concluded that all anastomosing canals within

65. Volkmann, R.: Arch. f. klin. Chir. **4**:436, 1863.

66. Zawisch-Ossenitz, C.: Ztschr. f. mikr.-anat. Forsch. **6**:76, 1926; **9**:585 and 606, 1927.

67. Pommer, G.: Ztschr. f. mikr.-anat. Forsch. **9**:540, 1927.

bone that have no smooth borders are perforating canals and that there is no need of distinguishing, as Pommer did, between true and false perforating canals. Furthermore, she observed that in the formation of perforating canals the bone ground substance a little in advance of the blood vessel or cellular sprout was in a stage which she called "preresorptive"; finally, she stated that the vessel in a perforating canal may degenerate and the canal then be filled with young bone or, more rarely, left empty.

In Pommer's polemic reply,[68] he reaffirmed his views concerning the perforating canals, and stated that the material which Zawisch-Ossenitz used in her investigations was not that best suited for such investigation, as it was mostly embryonal bone. For this criticism of her work there is some basis, as perforating canals in the sense that Volkmann described them are newly formed canals appearing in pathologic adult bone. In a discussion of the canals of blood vessels in normal and pathologic bone, I [69] attempted to clarify the distressingly confused issues concerning the nature and the mode of origin of pathologic canals. Nevertheless, such changes in the canals, although important in certain resorptive phenomena, are of minor significance in the resorptive picture of Recklinghausen's disease.

Pathogenesis of the Resorption of Bone in Hyperparathyroidism.—Herein it is my endeavor to explain the phenomena operating to produce the resorptive picture. As far as the bones are concerned, their resorption (decalcification, removal and thinning) depends on the extraction of minerals from their substance, causing a concomitant diminution in the actual bone substance. It seems probable to me that when the state of hyperparathyroidism is initiated, the minerals are first withdrawn from the soft tissues and excreted; this demands mobilization and withdrawal of the minerals from the bones, which partly compensates for the extraction of the minerals from the soft tissues. Hyperparathyroidism induces a state of acidosis, which requires compensation through the withdrawal of large stores of earthy alkaline substances from the bones. The manner in which the mineral stores are mobilized from the bones remains uncertain; there is, however, reason to believe that in hyperparathyroidism the tissue fluids circulating about the bone are so modified as to favor removal of minerals from the bone rather than their deposition. Following this decalcification, or halisteresis, osteoclasts proliferate to phagocytose the decalcified bone matrix, and marrow fibrosis ensues as part of the reaction to the changed status of the bone structure. It is evident that the continuation of such a state (chronic hyperparathyroidism, either clinical or experimental) leads to further

68. Pommer, G.: Ztschr. f. mikr.-anat. Forsch. **11**:283, 1927.
69. Jaffe, H. L.: Am. J. Path. **5**:323, 1929.

halisteresis, or decalcification, more pronounced resorption through osteoclastic proliferation and additional marrow fibrosis—all of which produce the advanced pathologic picture seen in Recklinghausen's disease.

Albright and Ellsworth [70] offered an explanation of skeletal decalcification which strikes me as failing to account for the initial source of change. Investigation of patients with clinical Recklinghausen's disease and patients with hyperparathyroidism induced by the injection of parathyroid extract-Collip led them to conclude that the basis for the pathogenesis of the decalcification is a disturbance of phosphorus metabolism. They coordinated the frequently depressed serum phosphorus level and the raised serum calcium level (in patients with clinical hyperparathyroidism) with a primary lowered renal threshold for excretion of phosphorus. In a number of papers [71] it was suggested that in both clinical and experimental hyperparathyroidism the increased excretion of calcium may be dependent on an increased excretion of phosphorus, leading to depletion of the phosphorus in the body fluids. As stated, they attributed the whole cycle of change primarily to a lowered renal threshold for phosphorus, induced by the hyperparathyroidism. However, the question is not so simple as these investigators would lead one to believe.

Their hypothesis presumes that the abnormality in the relation of the calcium ion to the phosphate ion in the serum in hyperparathyroidism is dependent on changes in the excretion of phosphorus through the urine. To them the state of hyperparathyroidism is first manifested by an increased urinary excretion of phosphorus. According to these workers, this is the beginning of a cycle which is marked by a decreased amount of inorganic phosphorus in the serum; this creates a tendency for subsaturation of the serum with calcium phosphate; this, in turn, leads to the mobilization of calcium phosphate from the bones to compensate; finally, the serum calcium level is raised, the urinary excretion of calcium is increased and the serum phosphorus level continues depressed because of the existence of the lowered renal threshold for phosphorus. These conclusions were based on metabolic studies of patients given injections of parathyroid extract-Collip. Their formula concerning the pathogenesis of the bone changes of clinical Recklinghausen's disease is based on these assumptions. They do not, however, give consideration to any of the numerous histologic phenomena that occur in the bones, nor do they explain how this apparent change in the renal threshold for phosphorus brings about the bone changes observed in hyperparathyroidism.

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70. Albright, F., and Ellsworth, R.: J. Clin. Investigation **7**:183, 1929.

71. Albright, Bauer, Ropes and Aub.[26] Albright and Ellsworth.[70] Ellsworth, R.: J. Clin. Investigation **11**:1011, 1932.

Furthermore, it is impossible to suppose that the rise in serum calcium after the injection of parathyroid extract-Collip is necessarily dependent on a decrease in serum phosphate—which inverse relationship is frequently accepted as the usual response following the injection of parathyroid extract-Collip in the normal dog or man. Thomson and Pugsley [72] more recently showed that in normal dogs the total serum inorganic phosphate may either increase slightly or remain constant after the injection of parathyroid extract-Collip. From their experiments they conclude that in the dog the rise in serum calcium after the injection of parathyroid extract is not secondary to a fall in the serum phosphate. If the renal threshold for the excretion of phosphate is affected, they believe that the change is not reflected in the composition of the blood. Bodansky and I [31b] demonstrated that the injection of a single moderate dose of parathyroid extract-Collip into puppies suffering from chronic hyperparathyroidism raised the serum phosphorus (within nine hours and earlier). Sometimes the increase of serum phosphorus was the earliest response in the blood and frequently the only response to a single injection of parathyroid extract-Collip in such dogs, while the serum calcium rose slightly, if at all. Thus, the assumption by Albright and Ellsworth that the lowered renal threshold leads to diminished serum phosphorus and increased serum calcium does not always hold.

Another theory has also been proposed: that hyperparathyroidism leads to decalcification of bone because the parathyroid secretion itself makes the plasma a better solvent for the bone minerals. Greenwald and Gross [27] suggested that an organic substance secreted by the parathyroid gland, identical with the parathyroid hormone formed under its influence, circulates in the plasma and unites with calcium ions to form an undissociated compound. According to them, the administration of parathyroid extract-Collip directly or indirectly increases this organic substance, thus reducing the concentration of calcium ions in the plasma and permitting the liberation of more calcium ions from the bone. This point of view would imply that the plasma behaves as if in equilibrium with the solid calcium-phosphorus compounds in the bone. It would be difficult to explain, on the basis of this view, how it is possible to attain a hypocalcemia with increased injections of parathyroid extract-Collip such as Bodansky and I [31b] observed in a dog on a low intake of calcium. Furthermore, the hypocalcemia was associated with a progression of the decalcification.

My colleagues and I therefore wish to reaffirm our own view, which attributes the entire sequence of changes that lead to the resorption of bone in hyperparathyroidism to a decalcification (halisteresis) caused by modified tissue fluids circulating about the bone. Only after this do other changes proceed in the bone. Extensive new bone formation occurs,

72. Thomson, D. L., and Pugsley, L. I.: Am. J. Physiol. **102**:350, 1932.

especially in rats, even while the resorption continues. On the other hand, Thomson and Collip [73] and Thomson and Pugsley [72] have held that the most acceptable theory of the action of parathyroid extract-Collip is that it directly stimulates the osteoclastic process. The osteoclasts, accordingly, erode the bone and liberate the mineral salts. They came to this conclusion because in experimental hyperparathyroidism numerous osteoclasts are to be observed in bone sections. Nevertheless, had they carefully studied large series of bone sections, they would frequently have found evidences of decalcification (halisteresis) before osteoclasts appeared. We agree with these authors that the changes in the bone in hyperparathyroidism are the result of local effects. However, we have found that osteoclasts arise to phagocytose the bone matrix only after it has been decalcified. We have also found that osteoclasts appear in as great numbers as they do in hyperparathyroidism under circumstances that cannot in any way be related to stimulation by parathyroid extract. Bodansky, Chandler and I [52] produced a histologic picture in many ways simulating that observed in chronic experimental hyperparathyroidism when we fed young, growing dogs a diet low in calcium (with or without the additional administration of ammonium chloride). Besides, in unpublished experiments, we also found that diets high in phosphorus which produced a marked disturbance in the calcium-phosphorus intake ratio also led to the appearance of numerous osteoclasts. This again could not be attributed to stimulation by parathyroid extract-Collip.

Relation of Certain Experimental Dystrophies to Those of Hyperparathyroidism.—Long before Recklinghausen's disease was recognized, experiments were undertaken on the dystrophic effects on the skeleton of calcium starvation. These experiments were instituted principally to ascertain the relation between experimental calcium deficiency and clinical rickets. Many of the early investigators who applied themselves to an experimental study of calcium deficiency believed that rickets had developed in their animals. Voit [74] fed puppies on fresh meat or meat extract, lard and distilled water. Deformities of the bones, especially of the legs, set in; there was curvature of the spine; the chest was flattened; the pelvis was narrowed and sunken; the animals were very weak, and after a hundred and fifty-three days they could not walk. At autopsy, there were multiple fractures and swelling at the costochondral junctions. On macroscopic grounds Voit considered the lesions as rachitic. The controls, receiving bone ash in addition, showed none of these lesions. It remained for Korsakoff [75] to point out that, although the macroscopic lesion produced in puppies on such a diet resembled

73. Thomson, D. L., and Collip, J. B.: Physiol. Rev. **12**:309, 1932.

74. Voit, E.: Ztschr. f. Biol. **16**:55, 1880.

75. Korsakoff: Zur Frage von der Pathogenesis der englischen Krankheit, Dissert., Moscow, 1883.

rickets, microscopically the lesion was not rickets, as the osteoid zones on the trabeculae were thin, and the epiphyseal cartilage plates were not markedly thickened. Miva and Stoeltzner [76] concluded that such lesions were of the nature of pseudorachitic osteoporosis, with fibrosis of the marrow. In the course of our studies, Bodansky and I [80a] fed young, growing puppies a calcium-deficient diet consisting of lean meat to which were added adequate quantities of tomato juice and cod liver oil (to protect the animals from rickets and scurvy). The animals grew well, but developed thin bones which fractured easily. After several months on this regimen, histologic examination of the bones showed extensive osteoporosis, considerable marrow fibrosis, some new bone formation in the marrow connective tissue, numerous osteoclasts in Howship's lacunae on the original and on the newly formed bones and slight widening of the proliferating cartilage zones. On the whole, the histologic appearance was different from what may be expected in rickets. The lesion, depending on its severity, ranged from a marked osteoporosis to a condition that could be distinctly called generalized osteitis fibrosa.

It is obvious that the gross and microscopic pathologic pictures as observed by the different investigators who studied the effects of calcium deficiency on the growing animal should have varied. Most earlier workers gave no consideration to the question of vitamin content. Some of the early investigators noted that the lesion appearing with a diet of lean meat plus carbohydrates were more severe than when the meat diet was supplemented with lard. Furthermore, variation in the fat content of the meat itself may account for some of the differences in the bone lesions, as muscle fat has a slight antirachitic potency. In harmony with this are the observations of Weber and Becks,[77] who fed growing puppies a synthetic diet, poor in calcium and free from vitamin D; they observed all the fibrous bone lesions described, plus giant cell tumors and pseudocysts about the roots of the teeth. This brings out the fact that the more drastic the diet, the more pronounced are the bone changes. In young dogs receiving an inadequate amount of calcium plus ammonium chloride (but protected against rickets and scurvy), Bodansky, Chandler and I [52] produced severe decalcification and resorption of bone and such marked marrow fibrosis that the resultant histologic picture could be designated as generalized osteitis fibrosa.

Thus, when there is a drastic deficiency of calcium due to an inadequate intake, the changes in the bones may, with some minor variations, approach those produced by chronic hyperparathyroidism. Hyperparathyroidism affects bones by abstracting their minerals. The ultimate effect of both treatments on the bones may show considerable similarity.

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76. Miva, S., and Stoeltzner, W.: Beitr. z. path. Anat. u. z. allg. Path. **24**:578, 1898.

77. Weber, M., and Becks, H.: Virchows Arch. f. path. Anat. **283**:752, 1932.

By this I do not mean to suggest that the two conditions are analogous. Hyperparathyroidism, while it abstracts the minerals from the bones, produces a hypercalcemia and often toxic changes in other tissues with metastatic calcification. On the other hand, the severe decalcification, resorption and fibrosis of the bones that result from a diminished intake of calcium are associated with a tendency for the level of the serum calcium to be below normal (sometimes tetany appears, owing to the hypocalcemia). The changes in the bones in both of these conditions are nothing more than an index of the calcium deficiency, produced, however, by two entirely different etiologic factors. While the bone lesions resulting from the administration of parathyroid extract-Collip are, in a broad sense, of the same histologic appearance as those produced in young, actively growing dogs on a diet low in calcium (but otherwise adequate), other important differences are noted. For instance, the dogs that are given parathyroid extract-Collip show stunting of growth, while those on a diet the calcium content of which is inadequate grow satisfactorily if the deficiency of calcium is not too drastic.

Relation of Generalized Osteoporosis to Generalized Osteitis Fibrosa.—One must conceive of generalized osteitis fibrosa as a rather inclusive category. Not only does it embrace the advanced clinical form of Recklinghausen's disease (which has a specific parathyroid etiology) and the experimentally produced osteitis fibrosa of similar origin; but it likewise covers the experimentally produced forms of generalized osteitis fibrosa which are caused by other means, and in which there is rapid resorption with resulting marked connective tissue proliferation in the marrow. Furthermore, in normal puppies, the amounts of calcium adequate for slow growth may, if these puppies are growing actively, produce a histologic picture of osteitis fibrosa different only in quantitative aspects from that which appears in rapidly growing puppies on a diet containing an inadequate amount of calcium. Thus, either clinically or experimentally, if decalcification of bone is rapid, no matter what the etiology—and this would apply either to the young or to the adult—generalized osteitis fibrosa occurs. From this point on there may be modification of both the gross and the histologic features of the osteitis fibrosa, owing to the special underlying factor inducing the decalcification. This makes it conceivable that hyperparathyroidism may, in the course of the development of osteitis fibrosa, incidentally favor extensive hemorrhage into the marrow, resulting in brown blood cysts and the formation of giant cell tumors. It is known that generalized osteitis fibrosa (Recklinghausen's disease) may exist without cysts and giant cell tumors.

On the other hand, a slowly developing decalcification, from whatever cause, will lead, in both the young and the adult patient, to a less severe resorption; this lesion is called osteoporosis, because of the

absence of striking fibrosis. The occurrence of osteoporosis in adults under a number of circumstances is well known, and one of the most common causes, aside from senility, is exophthalmic goiter. In this disease there is a negative mineral balance, but the patients usually do not suffer from the effects of a diminished intake of calcium. The disease is chronic and the resorption is slow but progressive.

The modifying effects of several factors on the bone lesion are further illustrated in experimental rickets. It is well known that rickets cannot be produced experimentally in rats by withholding vitamin D unless there is simultaneously a dietary mineral imbalance (disturbance of the calcium-phosphorus ratio). In very young, rapidly growing rats given a curative vitamin D supplement but a diet low in calcium a generalized osteitis fibrosis will develop. On the same regimen with much more vitamin D (short of toxic dosage) the marrow fibrosis will be essentially prevented, and simple generalized osteoporosis will ensue. The same diet with the exclusion of vitamin D will produce rickets. In addition, the greater the disturbance of the calcium-phosphorus ratio in the diet, the larger are the requirements for vitamin D.[78] These commentaries explain the development of the pathologic picture of osteoporosis rather than osteitis fibrosa or vice versa; the difference depends chiefly on the celerity with which the resorption occurs.

While the experiments noted have yielded comparisons mostly on regimens low in calcium and high in phosphorus, it is recognized that similar results can be obtained with a different type of calcium-phosphorus imbalance, namely, a diet of low phosphorus and high calcium content. It is well known that in certain regions where the grass has a low phosphorus content, osteophagia develops in cattle, with extreme skeletal decalcification and increased serum calcium and low serum phosphorus values.[79]

The changes in the bones of animals with spontaneous osteitis fibrosa resemble in many ways, but frequently do not duplicate, those observed in the fibrous osteodystrophies of man. Peculiar to some animals with fibrosed bones is the common appearance of obstruction of the nasal and oral cavities; these are encroached on by thickening of their walls. As a result, such animals may have sniffling respiration. However, fibrous lesions of the bones exist in animals not afflicted with sniffling respiration. Christeller,[51] Rehn,[80] Hintze,[81] Busolt [82] and Ingier [83]

78. Bethke, R. M.; Kick, C. H., and Wilder, W.: J. Biol. Chem. **98**:389, 1932.

79. Palmer, L. S., and Eckles, C. H.: Proc. Soc. Exper. Biol. & Med. **24**:307, 1927. Robertson, W.: J. Comp. Path. & Therap. **18**:114, 1905.

80. Rehn, E.: Beitr. z. path. Anat. u. z. allg. Path. **44**:274, 1908.

81. Hintze, R.: Arch. f. wissensch. u. prakt. Tierh. **35**:535, 1908-1909.

82. Busolt: Schnueffelkrankheit der Schweine, Dissert., Giessen, 1913.

83. Ingier, A.: Frankfurt. Ztschr. f. Path. **12**:270, 1913.

described swine, goats, cattle and horses which showed either true generalized osteitis fibrosa or a local form of osteitis fibrosa. In most instances only the skull was studied, but in a limited number a complete examination of the skeleton was made, and generalized osteitis fibrosa was found. Koch [84] and Christeller observed spontaneous osteitis fibrosa in monkeys, Koch pointing out that the condition had been previously confused with rickets.

Dogs are also subject to spontaneous osteitis fibrosa. Christeller described a dog the bones of which were thin and porotic, the long tubular bones showing curvature and diminished longitudinal growth. The lesions were most prominent in the upper and lower portions of the diaphyses, where there was fibrous replacement of the marrow, transformation of the existing bone, new bone formation and resorption of bone with numerous Howship's lacunae and osteoclasts. The haversian canals of the cortex were widened and invaded by fibrous tissue. The epiphyseal cartilage plates were present, and relatively normal endochondral ossification was still in progress. The entire skeleton was involved, but the ribs relatively showed the greatest alterations. Schmey [85] and Pick [86] described an atrophic deforming generalized disease of bone in senile dogs with a predominance of osteoporosis but with little fibrosis. Hager [87] described an instance of osteitis fibrosa in a dog in which the upper and lower jaws were tremendously enlarged. Weber's [88] dog, 8½ months of age, had spontaneous fibrous osteodystrophy with thickened porotic bones, cysts and giant cell tumor formations. The jaw of the dog was also enlarged and cystic. The parathyroids were normal, and calcium metastases were not observed.

It is difficult to attribute any specific connotations to this miscellaneous collection of spontaneous fibrotic diseases in animals. Often the examination was made by one who saw the bones only after the animal's death; frequently no history was available. It is fair to surmise that some fundamental disturbance in metabolism was at the root of the changes described. If not a disturbance in mineral intake, it may have been a condition related to a disturbance of the gastrointestinal tract (such as diarrhea, which in effect could produce the same changes). The sniffling respiration is a complication that is to be attributed to local infection in an animal suffering from the bone lesions indicated.

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84. Koch, J.: Verhandl. d. deutsch. path. Gesellsch. **13**:107, 1909.
85. Schmey, M.: Virchows Arch. f. path. Anat. **220**:52, 1915.
86. Pick, L.: Berl. klin. Wchnschr. **68**:797, 1911.
87. Hager, O.: Ueber einen Fall von Ostitis fibrosa beim Hunde, Dissert., Giessen, 1919.
88. Weber, M.: Beitr. z. path. Anat. u. z. allg. Path. **82**:1, 1929.

The Parathyroid in Recklinghausen's Disease.—In the introduction of this paper, the evolution of knowledge concerning the relation of parathyroid enlargement to diseases of bone was traced. Emphasis was laid on the various advances leading up to the present understanding of the subject, and an evaluation was made of the significance of these contributions. From all these emerged one fact of dominating importance: *Parathyroid enlargement with parathyroid hyperactivity was proved to be the primary basis (both etiologically and pathogenically) for generalized osteitis fibrosa cystica, or Recklinghausen's disease.*[89]

Accumulated postmortem and clinical experience with this disease demonstrated the variability of the number, size, position and gross and histologic appearance of such enlarged parathyroid glands. Postmortem experience has also shown that in some cases one enlarged parathyroid gland was the only parathyroid tissue found, even in careful dissection; in other cases one or more (in some instances even four) normal parathyroid glands were found, even in the presence of an offending enlarged parathyroid. When normal parathyroid glands were not

89. It is rather amazing that in spite of the accumulated evidence, on pathologic, clinical and experimental grounds, that Recklinghausen's disease is distinct and separate from other malacic diseases (as for instance, osteomalacia and osteoporosis), there are many who as yet do not accept it as an entity. Looser, even as late as 1928, stated that cysts and giant cell tumors of bone (whether solitary or multiple) are local posttraumatic formations, which occur both in normal and in extensively diseased bone (Looser, E., in Schinz: Lehrbuch der Röntgen-Diagnostik mit besonderer Berücksichtigung der Chirurgie, Leipzig, Georg Thieme, 1928, p. 243). He could not accept their presence in a malacic condition of bone as indicating a special disease. To him, fibrous osteitis was only a symptomatic process that might be produced by many conditions; therefore, since cysts and giant cell tumors, if present, were not significant as indicating a particular feature of the malacic disease, Recklinghausen's disease per se could not exist. Looser's conclusions concerning the mode of origin of cysts and giant cell tumors were based on roentgenologic examinations; similarly his conclusions concerning Recklinghausen's disease were not based on pathologic studies. By 1932, he was impelled to modify this stand, accepting Recklinghausen's disease as an entity. Lang and Häupl (Virchows Arch. f. path. Anat. **282:**383, 1926) stated that the pathologic changes of Recklinghausen's disease are simply the result of pathologic irritation of poorly calcified bone, and that similar changes may be observed in the bone and bone marrow in osteoporosis, osteomalacia and rickets. Lang (Beitr. z. path. Anat. u. z. allg. Path. **87:**142, 1931), reaffirming this stand, added that the osteitis fibrosa of Recklinghausen's disease is nothing else than the consequence of bone and marrow fibrosis subsequent to pronounced osteoporosis. In regard to the view of Lang and his co-worker, there can be no doubt that the fibrous tissue reaction in rickets and osteomalacia is the consequence of mechanical and static deficiencies in weakened bone. To stretch the explanation of the nature of the connective tissue response in these diseases to cover the connective tissue response in Recklinghausen's disease as being of no other significance seems far fetched in view of the established parathyroid pathogenesis for the latter condition.

found, it is conceivable that they had undergone involutional atrophy because of the presence of an enlarged hypersecreting gland. It is equally possible that the enlarged parathyroid was the only one formed embryologically. In any event, these pathologic findings indicate the danger of parathyroid tetany following operative removal of an enlarged gland. One of the striking features so far brought out in the studies of the relation of parathyroid tumors to Recklinghausen's disease is that they are benign. There is danger of interpreting a benign tumor as malignant, as Wellbrock[90] did, because of certain atypical histologic appearances.

The variability in the size and weight of the parathyroid tumor (or tumors) has been considerable; they have measured from 1 to 7 cm. in the greatest diameter; each of the two adenomas in Paul's case weighed as much as 35 Gm.[91] No correlation has been established between the size of the offending parathyroid tumor and the severity of the disease. In spite of their large size, it is amazing that so few of them could be palpated before operative removal; some of the largest glands were not palpable because they were tucked away behind the thyroid (between the esophagus and trachea).

The parathyroid tumors are often diversely situated, sometimes far removed from the expected position; this is quite in accord with the fact that even the normal parathyroid glands may vary extremely in their anatomic locations. Hypersecreting parathyroid adenomas have even been found completely within the substance of the thyroid gland, as well as in the mediastinum.

The enlarged parathyroid gland is usually nodular and cystic; microscopic cysts predominate (such cysts may even be observed in normal parathyroid glands), but frequently the cysts are large enough to be recognized grossly; the cut surface appears yellowish. The microscopic appearance of such an enlarged parathyroid may in places be so changed as to lose all semblance of normal parathyroid tissue. In such areas, the cells and also the nuclei are usually very much enlarged; giant or multiple nuclei may be observed within some of the enlarged cells. In such abnormal areas, the protoplasm of the cells may show varying degrees of density. Even within these areas, nests of water-clear principal cells may be seen. Among the other appearances that may sometimes be observed are alveolar formations with colloid-like contents, foci of small cells with pyknotic nuclei and any number of other abnormalities induced by degeneration within the enlarged gland. In the nondegenerated areas of the parathyroid tumor, the principal cell usually predominates. However, some of the para-

90. Wellbrock, W. L. A.: Endocrinology **13**:285, 1929.
91. Paul, F.: Beitr. z. path. Anat. u. z. allg. Path. **87**:503, 1931.

thyroid tumors have been described as composed, for the most part, of oxyphil cells; it seems nevertheless beyond doubt that the oxyphil cells are derived from the principal cells, and that pale oxyphil cells can lose their histologic peculiarities and become indistinguishable from the ballooned-out principal cells. Even when either the principal or the oxyphil cells predominate, some of the other cells are usually to be seen. Most of the tumor cells are free from fat, but if fat is present in them it exists in the form of fine granules.

Discussion as to whether the parathyroid tumor is the result of a compensatory hyperplasia or whether it is an adenomatous new growth seems to me to have been entirely settled in favor of the latter. This view is supported by the fact that removal of such tumors in Recklinghausen's disease leads to prompt clinical improvement, with correction of the bone lesions, when all the offending tissue is extirpated. For the sake of discussion, one may, of course, grant that in glandular organs compensatory hyperplasia may be histologically indistinguishable from adenomatous new growths. The usual gross anatomic distinction that is made in regard to an adenoma (that it is an encapsulated spherical mass situated within the tissue in which it arises) does not necessarily apply to the parathyroid gland. It must be plainly evident that an adenoma arising in a parathyroid gland may grow to such proportions as completely to destroy and replace the tissue in which it originated.

Compensatory Parathyroid Enlargement: In Recklinghausen's disease, the enlarged parathyroid is a tumorous new growth; but parathyroid enlargement may occur under a number of circumstances on the basis of a compensatory reaction. This is occasionally observed in genuine osteomalacia. A similar explanation seems to hold for the parathyroid enlargements that may at times occur in certain cases of senile osteoporosis, hunger osteopathy, multiple myeloma, clinical and experimental rickets and chronic nephritis, and in the presence of multiple carcinomatous skeletal metastases. In such cases, the enlargement generally involves all four, or the two main glands, but may be limited to only one. The last form is the least common. MacCallum [17] observed a cystic parathyroid mass, 2 cm. in diameter, in a young man who suffered from chronic nephritis for years. The enlarged parathyroid was opaque and whitish yellow, and on microscopic section differed in no way from normal parathyroid tissue, except that no fat cells were present between the cell strands. The pathogenesis for such enlargement cannot be definitely assigned; it may possibly be the index of an effort to secrete more of the active parathyroid principle (which, within certain physiologic limits, undoubtedly exercises a beneficial effect on calcium metabolism and aids in the absorption of minerals from the intestinal tract). The secretion at the same time probably assists in a better economy of these minerals after absorption;

possibly it helps in the maintenance of normal serum calcium values when abnormal drainage of the mineral stores takes place.

Malignant Parathyroid Growths: It is difficult to decide whether malignant tumors of the parathyroid occur. The tumors described by Benjamins [92] and Hulst [93] were located within the thyroid gland; they had been removed surgically; no mention was made of the condition of the bones. Such tumors exhibit local malignant characteristics and may metastasize. Langhans [94] designated them as "parastruma"; they are probably carcinomas of the thyroid; within their substance they may show thyroid tissue; histologically their cells resemble the principal cells of the parathyroid. It therefore remains doubtful whether malignant tumors of the parathyroid gland have thus far been reported.

Other Tissue Changes in Recklinghausen's Disease.—Metastatic calcification is the significant pathologic alteration that has been noted in the soft tissues in some cases of hyperparathyroidism. In Dawson and Struthers' [20] case, calcium deposits, in the form of fine granules, which in some instances became confluent masses, were present in all the internal organs and in all tissues of the body. The arteries in their case were also calcified. This was an unusually pronounced example of metastatic calcification; more frequently, if present at all, it is limited to the lungs, gastric mucosa and kidneys. Since metastatic calcification was first recognized, these sites have been known to be favored for the depositions. Their predisposition to the precipitation of salts of calcium is attributed to the existence of an intense local alkalinity in these tissues as they are sites of considerable acid excretion. In the lungs, the calcific deposits are observed mainly in the connective and elastic tissue of the alveolar walls, in the capillary walls and sometimes in the elastic fibers of the small arteries and veins; in the gastric mucosa, the interglandular tissue is chiefly infiltrated, especially in the acid-secreting portion; in the kidneys, calcium is deposited especially in the tubular epithelium, although the connective stroma may demonstrate calcific incrustations.

Since Virchow's [95] original description of metastatic calcification, it has been held that renal disease seems to be a necessary concomitant for the production of the calcium deposits. Barr [96] recently reviewed this subject, collecting forty-two instances of miscellaneous spontaneous metastatic calcification. In this varied group, he noted that the absence of renal involvement was exceptional. Dawson and Struthers' patient, with metastatic calcification of most intense degree, did not have nephri-

92. Benjamins, C. E.: Beitr. z. path. Anat. u. z. allg. Path. **31**:143, 1902.
93. Hulst, J. P. L.: Centralbl. f. allg. Path. **16**:103, 1905.
94. Langhans, T.: Virchows Arch. f. path. Anat. **189**:69, 1907.
95. Virchow, R.: Virchows Arch. f. path. Anat. **8**:103, 1855.
96. Barr, D. P.: Physiol. Rev. **12**:593, 1932.

tis. The deposition of calcium in the lungs of the new-born (on a congenital basis) has occasionally been reported.[97] There is still uncertainty as to whether local tissue damage precedes the calcific depositions. Those who favor its occurrence believe that the overloading of the tissue fluids with calcium is insufficient in itself to determine the deposition of the mineral, even in sites of intense local alkalinity. At the present time, no all-embracing explanation of the phenomena underlying metastatic calcification can be offered.

While metastatic calcification is extremely rare as a postmortem finding, it was recently discovered that it could easily be produced with toxic doses of parathyroid extract-Collip or viosterol. In the dog, overdosage of parathyroid extract produces vomiting, diarrhea, hematuria, hemorrhagic gastro-enteritis, renal impairment and metastatic calcification in the soft tissues (especially in the kidneys, lungs and gastro-intestinal tract).[98] Metastatic calcification was observed in the dogs dying of acute experimental hyperparathyroidism which my colleagues and I examined. When we studied dogs which were suffering from chronic hyperparathyroidism (but which had completely recovered from any acute hyperparathyroidism that may have existed previously), we found metastatic calcification completely or virtually absent at autopsy. We interpreted this as indicating that the metastatic calcifications which probably had been present in these animals earlier were resorbed during the chronic stage of the hyperparathyroidism.

With toxic doses of viosterol the effects are quite similar, but the tendency to calcification of blood vessels seems to be greater than in hyperparathyroidism. Kreitmair and Moll[99] demonstrated calcium deposits of such degree that the walls of large and small blood vessels were stiff and tubelike. The calcification was most intense in the media, although the other coats may have been involved. With enormous single doses of viosterol, Ham[100] produced in the rat massive calcifications in the aorta, coronary vessels and cardiac musculature as early as forty-eight hours after administration. Shohl, Goldblatt and Brown[101] fed doses of viosterol that killed their young rats in from five to fourteen days. They observed parenchymatous degeneration, necrosis, inflammatory infiltration and calcification in various organs (mainly, however, in the tubules and vessels of the kidney, the muscle and vessels of the heart and the muscularis and mucosa of the stomach); calcification appeared with moderate frequency in the lungs and aorta

97. Bross, K.: Centralbl. f. allg. Path. u. path. Anat. **49**:229, 1930.
98. Hueper, W.: Arch. Path. **3**:14, 1927.
99. Kreitmair, H., and Moll, T.: München. med. Wchnschr. **75**:637, 1928.
100. Ham, A. W.: Arch. Path. **14**:613, 1932.
101. Shohl, A. T.; Goldblatt, H., and Brown, H. B.: J. Clin. Investigation **8**:505, 1930.

but rarely in the suprarenal glands. Roentgenologically, the bones of their rats showed rarefaction of the shafts; microscopically, the ribs showed thinning of both the cortex and the spongiosa. Soeur,[102] working in this laboratory, found that large doses of viosterol demineralized the bones of guinea-pigs, but the resorption was not severe enough to induce great degrees of marrow fibrosis. Grauer,[103] feeding large doses of viosterol to young guinea-pigs, induced much more severe demineralization, the resorption of bone being associated with considerable marrow fibrosis.

In spite of the fact that, histologically, resorption of the bones (and therefore demineralization) was noted by a number of investigators, Jones and Robson [104] stated that the ash content of the femora of young and old rats given large doses of viosterol was not especially different from that of their controls. Without the least reflection on the correctness of the chemical analyses made by these workers, it should be pointed out that the rat has a special tendency to react to substances like viosterol by the appearance of an osteosclerosis in the metaphyses. Extensive pathologic changes may therefore exist in a bone, with no significant alteration in the ash content, owing to the substitution of new bone for the resorbed bone.

With regard to the metastatic calcification produced by toxic doses of parathyroid extract-Collip or viosterol, the same controversy has arisen as in the case of spontaneous metastatic calcification. This controversy hinges on the same question, as to whether the degeneration of the tissues precedes the deposition of the calcium salts. Ham [100] does not believe that the depositions depend on degenerative changes in the tissues. However, Shohl, Goldblatt and Brown [101] found that irritative and toxic processes were associated with the decalcification. They could not be certain whether such changes always preceded the deposition of the calcium salts. In this connection, Shelling [105] stated that the composition of the diet fed to rats, with respect to the calcium and phosphorus content, is a determining factor in the toxicity and hypercalcifying property of viosterol. He found that large amounts of phosphorus in the diet, in the presence of viosterol, render the tissues more susceptible to metastatic calcification. He claimed that rats fed a diet of a high calcium and low phosphorus content and given toxic doses of viosterol may die without evidences of metastatic calcification, although hypercalcemia exists.

The fact that parathyroid extract-Collip and viosterol in toxic doses both produce metastatic calcification, hypercalcemia and hyperphos-

102. Soeur, R.: Arch. internat. de méd. expér. **6**:1, 1931.
103. Grauer, R. C.: Proc. Soc. Exper. Biol. & Med. **29**:466, 1932.
104. Jones, J. H., and Robson, G. M.: J. Biol. Chem. **91**:43, 1931.
105. Shelling, D. H.: Proc. Soc. Exper. Biol. & Med. **28**:298, 1930.

phatemia has led to much speculation as to the manner in which they bring about these effects. Taylor, Weld, Branion and Kay [106] held that toxic doses of viosterol accomplish their injurious effects, including calcium metastases, through stimulation of the parathyroid glands. Harris [107] and many others disputed this view, holding that no evidence has been offered in its favor. In fact, it is known that toxic doses of viosterol will produce all of their effects even after extirpation of the parathyroid glands. Taylor and Weld [108] further held that large doses of viosterol depress the power of the intestine to excrete calcium; the calcium which it mobilizes from the bones accumulates in the serum and is excreted through the kidneys. On the other hand, Bauer, Marble and Claflin [109] found that the beneficial effects of therapeutic doses of viosterol are to be attributed to the intake of calcium and not to stimulation of the parathyroids.

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106. Taylor, N. B.; Weld, C. B.; Branion, H. D., and Kay, H. D.: Canad. M. A. J. **24**:763, 1931.

107. Harris, L. J.: Lancet **1**:1031, 1932.

108. Taylor, N. B., and Weld, C. B.: Brit. J. Exper. Path. **13**:109, 1932.

109. Bauer, W.; Marble, A., and Claflin, D.: J. Clin. Investigation **11**:47, 1932.

(To be Concluded)

Notes and News

Awards.—The honorary degree of doctor of science has been conferred by the Ohio State University on Edward Francis of the National Institute of Health, Washington, D. C.

The Dutch Red Cross Society has awarded its gold medal to Karl Landsteiner, member of the Rockefeller Institute for Medical Research, for his discovery of the blood groups.

Society News.—The American Society of Clinical Pathologists has elected the following officers for 1933-1934: president, A. G. Ford; president-elect, F. H. Lamb; vice-president, J. J. Seelman; secretary-treasurer, A. S. Giordano (South Bend, Ind.).

An International Congress on the Scientific and Social Fight Against Cancer will be held in Madrid, Oct. 25 to 30, 1933, under the auspices of the Spanish League Against Cancer. The secretary is Julio Bejarano, Atocha, 104, Madrid.

A plenary meeting of the Société Anatomique de Paris will be held in Paris on Oct. 12 and 13, 1933. The two subjects for special discussion are cerebral hemorrhage and the medicosurgical anatomy of the nervous peduncles of the visceral apparatus. The secretary is Dr. René Huguenin, 21, rue de l'Ecole-de-Médecine, Paris (VI).

Consent for Necropsy of Child.—A verdict in favor of Harvey S. Thatcher and Albert F. De Groat of the department of pathology in the University of Arkansas has been rendered in the suit against them on account of necropsy on a child. The mother of the child had signed the permit for the necropsy, but the father had not although he was present at the time. Hereafter both parents will be required to sign permits for necropsy, as they are joint guardians under the laws of Arkansas.

Obituary

WILLIAM THOMAS COUNCILMAN

1854-1933

Dr. Councilman's great great grandfather, Christopher Councilman, came from Holland and settled in Baltimore County, Md., early in the eighteenth century. From him descended the Councilmans and Counselmans of America. His mother was Christiana Drummond Mitchell, of English and Scotch descent. Her father was a lawyer and judge, and her mother, Elizabeth Crane, a daughter of Col. Thomas Crane of the English army.

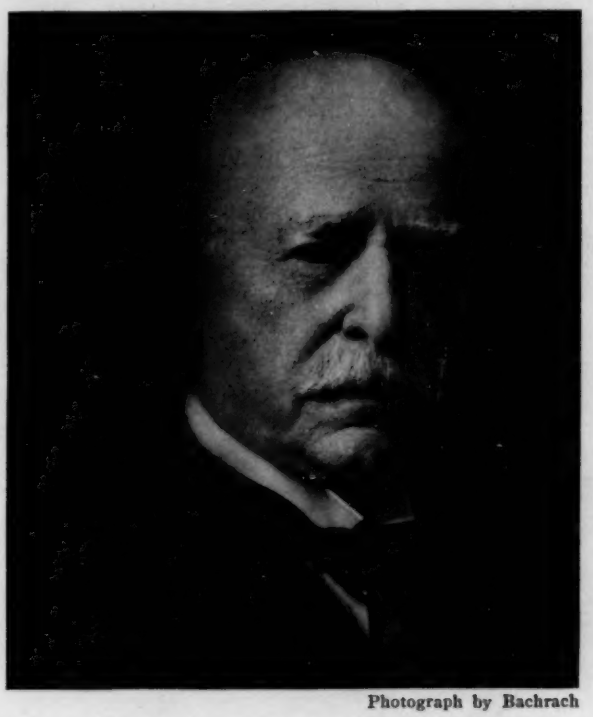
The Councilmans of Baltimore County were sturdy, energetic and independent farmers, public-spirited and influential in the development of horticulture. Dr. Councilman's father, a graduate in medicine from the University of Maryland, practiced medicine for a few years in Calvert County, Md., in the village of Friendship. In 1852 he moved to Pikeville and settled on part of the family land, about sixty acres, and, like other physicians of that region and period, directed farming operations while engaged in the active practice of medicine. On this farm Dr. Councilman was born on Jan. 1, 1854. There his barefooted boyhood was spent. He fished, hunted and assisted at chores; absorbed interest in horticulture and gardening from his father and mother; acquired respect for agricultural achievement, and above all, a great love for creative gardening, which he practiced throughout his life.

Dr. Councilman's education began at home; at 7 years of age he went to the district school, and at 10 years, to St. Thomas School (Episcopalian), which required a daily three and a half mile tramp each way. In 1867, at the age of 13, he entered the first preparatory class of St. John's College, Annapolis, which he left when 16 years old, at the end of his sophomore year. Stimulated by his brother Charles, he took a position with a firm in the business of importing and jobbing coffee and sugar. Then he had a brief venture by himself in Charlestown with some success, but eventually distaste. Soon, at his father's suggestion, he took up the study of medicine at the University of Maryland, obtaining the degree of M.D. in 1878, still young in years, only 22, but having had unusual contacts with the realities of life.

The opening of Johns Hopkins University and Huxley's address in 1876 made a great impression on him. In the spring before his graduation he came in contact with Henry Newhall Martin, professor of

physiology at Johns Hopkins University, and learned to use a microscope, did work in experimental physiology and saw research in progress.

After graduation, he became assistant quarantine officer of Baltimore. With the first money earned he purchased a microscope, and his work which Martin saw on a visit to the station led to an assistantship in physiology at Johns Hopkins University and participation in the conduction of a course in general biology. The following summer, again at the quarantine station in order to earn money for a trip abroad, he



Photograph by Bachrach

WILLIAM THOMAS COUNCILMAN

1854-1933

made studies on the origins of cells in the inflamed cornea, which won a prize of one hundred dollars offered by the leading medical society of Baltimore. The winter of 1879-1880 was spent at Bay View Asylum. After another summer at the quarantine station he had, in November, 1880, sufficient funds for travel abroad.

At Vienna he was rebuffed by Stricker, who did not like Councilman's statements, contrary to his own, regarding the origins of cells in inflammation. He obtained a place with Chiari for the winter, and in the spring he went to Leipzig and worked with Cohnheim and

Weigert; thence he went to Strassburg and von Recklinghausen. In May, 1882, he returned to Vienna for more work with Chiari and Kaposi. In October, 1882, he returned and obtained a fellowship at Johns Hopkins University, was associated with Sternberg in bacteriologic work, and for the next few years taught in the two medical schools in Baltimore, the Maryland University and the College of Physicians and Surgeons. He performed postmortem examinations at Bay View, and wrote short papers, one with Abbott on malaria and one entitled "The Microscopical Investigation of the Brain and Spinal Cord."

In 1886, he joined Dr. Welch as associate in pathology. In 1888 he went abroad for another year of study in preparation for his appointment as assistant professor of pathology and resident pathologist at Johns Hopkins Hospital. The classic monograph with Lafleur on amebic dysentery published in 1891 is his best known work of this period and is extensively illustrated with drawings made by himself. The years 1889-1892 at Johns Hopkins University brought him into intimate daily association with Welch, Osler, Halsted and Mall.

Dr. Councilman's election as Shattuck professor of pathological anatomy at Harvard University came in 1892. Hitherto Boston and the Harvard Medical School had reared their own professors; the departure from custom was a mark of special distinction and focused attention on him. He probably achieved what was expected of him, for he brought new life into the school. Appointed visiting pathologist to the Boston City Hospital in 1892, he organized the laboratory there and drew Mallory into the field of pathology. Within a year he boldly wrote the trustees of the Massachusetts General Hospital that they needed a pathologic department "with a full time salaried pathologist in charge," and so, when in 1896, a building for the purpose was completed, he recommended James Homer Wright, who became the first "Pathologist and Director of the Clinical Laboratory" of that famous institution.

Perhaps the most important of Councilman's innovations was keeping "open house" in his department. He made opportunities to work in pathology attractive by his enthusiasm and drew to him and into the field of pathology many men now holding professorships in pathology or medicine. He was constantly on the watch in the classroom for students of ability. He fostered the development of Southard and finally the establishment of a separate department of neuropathology.

As a teacher, he was stimulating through his enthusiasm. His lectures were never dull, and were always illuminated by blackboard sketches and enlivened by his whimsical humor. In earlier years the students probably got considerable enjoyment from his explosive enunciation of certain terms such as "polymorphonuclear leukocyte" because

of his tendency to stammering and his fiery determination to overcome it. Life in contact with Councilman was never dull. He married Isabella Coolidge of Boston in 1894, and until his children reached an imitative age, expressions of interest and enthusiasm as well as of anger were apt to be accompanied by very pungent and forcible expletives. At times he would seek companions for a visit to the Art Museum or the Arnold Arboretum which he loved and knew thoroughly, and in the spring of the year for supper and Bock beer, and on holidays, at any season, for walking excursions into the country for pistol practice and lunch of bread, chops and bacon toasted on green sticks over an open fire. He was a "crack shot" with pistol and revolver and practiced with them throughout his life.

His memory was extraordinary, and at sight of an unusual specimen he could refer to helpful articles in *Virchow's Archives* and *Ziegler's Beiträge* by page and volume.

In teaching, he emphasized the laboratory side and endeavored always to improve that part of the course for students. He stressed learning to observe and to do rather than the acquisition of facts.

His most important work at Harvard University was his influence on teaching. His duties as administrator and teacher and in the hospital were constantly heavy, and his list of publications is not a long one. When the Peter Bent Brigham Hospital opened in 1913, he took over the pathologic department with great enthusiasm, even forsaking in the first years his family and beloved gardens at York Village, Me., during part of the summer vacations. For Buck's "Reference Hand Book of the Medical Sciences," he wrote articles on glanders, rhinoscleroma, tuberculosis and inflammation. His best known scientific contributions are a study on nephritis in 1897, an article on epidemic cerebrospinal meningitis with Mallory and Wright in 1898 (a monograph published as a report of the State Board of Health of Massachusetts), an article on diphtheria with Mallory and Pearce in 1900, and the large monograph on the pathology and etiology of variola and vaccinia with Magrath, Brinckerhoff, Tyzzer, Southard, Thompson, Bancroft and Calkins in 1904. This splendid monograph, probably the best ever written on the pathology of smallpox, has not received the credit it deserves. In spite of the wealth of pathologic observations and experimental studies it contains, one finds it too little consulted, probably because of the association in the minds of workers with overemphasis on the inclusion bodies (Cytoryctes variolae) of Guarnieri. The real value of the work dropped because of the fall in news value which came with the nonacceptance of Cytoryctes.

Dr. Councilman also wrote numerous addresses, one about Osler, the others pertaining to medical education and stressing the importance

of the laboratory methods in teaching. With F. B. Mallory he wrote a "Syllabus of Pathology," published in 1904 by J. L. Fairbanks Company of Boston. Later he wrote a larger volume, "Pathology, A Manual for Teachers and Students," published in 1912 by W. M. Leonard of Boston. "Disease and Its Causes" was published in 1913 as one of the series of The Home University Library of Modern Knowledge by Holt and Company.

He was a member of the Council on Medical Education of the American Medical Association from 1904 to 1909, and a member of the Board of Trustees from 1909 to 1917.

In 1916 Dr. Councilman and Dr. R. H. Lambert went as medical observers up the Amazon River with Dr. A. Hamilton Rice's expedition. The medical report of the expedition, which appeared in 1918, reproduces many photographs by Dr. Councilman, and reveals that he was as much interested in the forests as in the diseases of the human inhabitants of the regions traversed.

He returned from the expedition with impaired health and thereafter suffered from attacks of angina, which in no way seemed to depress him or diminish his enthusiasms over his favorite interests and hobbies. In 1917, because of the retiring age of 63, he left the Brigham Hospital. In 1919 he went to Pekin, accompanied by Mrs. Councilman, as temporary professor of pathology at the Union Medical College. There he remained for two enjoyable years. He resigned from his professorship at the Harvard Medical School in 1923. His last scientific interest was in the symbiotic fungi in root hairs of plants and trees. In the few years before his retirement from teaching and for several years afterward a microscope accompanied him always when he was traveling. A friend once surprised him over a microscope studying root hairs in the band-stand in a park in Los Angeles. His final paper, published in the Proceedings of the National Academy of Science in 1923, was entitled "The Root System of Epigaea Repens and Its Relation to the Fungi of the Humus."

During the last ten years of his life he lived during the growing seasons at York Village, Me., where every tree, vine, shrub and plant on his place had been planted by him. He worked in his gardens up to the day of his death. A legacy from him which will be long cherished is about six hundred yards of iron paling fence on the Van Dyke Street side of the Peter Bent Brigham Hospital which he personally planted with his favorite climbing roses soon after the hospital buildings were erected.

One never knew how much Dr. Councilman cared about honors. That he enjoyed the opportunities for effective service offered by the presidency of the board of trustees of the American Medical Association was quite evident. A large gold medal given to him by some society

has for years reposed in a desk in a storage warehouse. None of his colleagues ever heard Dr. Councilman mention the honor. He was a fellow of the American Academy of Arts and Sciences, fellow of the Philosophical Society of Philadelphia and member of the National Academy of Sciences. His honorary degrees were A.M., Harvard University, 1899; A.M., Johns Hopkins University, 1902; LL.D., University of Maryland, 1907; LL.D., McGill University, 1911; LL.D., Western Reserve University, 1929; LL.D., St. John's College, 1932.

He is survived by Mrs. Councilman and three daughters, Mrs. W. O. Morgan and Mrs. Frank Wigglesworth, both of Cambridge, Mass., and Dr. Elizabeth Councilman, a graduate of Columbia University College of Physicians and Surgeons and now of Bellevue Hospital, New York.

Dr. Councilman was a sturdy, kindly, observant character. He practiced the amenities of life unadorned by formalities or artificialities. His personality stood naked before all. He cultivated neither reserve nor mannerisms; he achieved dignity unconsciously by virtue of directness, competence and honesty. In his pupils he inspired respect and admiration and in the highest degree, affection. He understood the nature of man as thoroughly as he understood trees, and his appraisal of men was rapid, accurate and tolerant, because he expected faults, particularly selfishness of which he was so free. His sources of satisfaction were many: in affectionate family life, in achievement in work and in recreative fields and in the progress of men to whose careers he gave impetus.

S. B. WOLBACH, M.D.

Abstracts from Current Literature

Pathologic Anatomy

CARDIAC HISTOPATHOLOGY IN THYROID DISEASE. C. V. WELLER, R. C. WANSTROM, H. GORDON and J. C. BUGHER, Am. Heart J. **8**:8, 1932.

A morphologic study of the hearts of thirty-five patients with exophthalmic goiter showed, with but few exceptions, no gross or microscopic pathologic changes not equally represented in a carefully matched control series. The exceptions found were: (1) a relatively higher incidence of myocardial fibrosis, endocardial sclerosis and cellular infiltrations in the series with exophthalmic goiter, and (2) one case in the series of thirty-five which showed an active focal myocarditis in which no etiologic factor could be ascertained other than the hyperthyroid state. Twenty-eight, or 80 per cent, of the exophthalmic series showed areas of myocardial fibrosis, as compared with 51.5 per cent of the control series. It is impossible to determine to what extent, if any, such areas of fibrosis may be the result of an active myocarditis of the type found in the single case. The hearts of fifty-five patients with adenomatous (nodular) goiter failed to show any significant difference in the incidence of pathologic changes as compared with a matched nongoitrous control series.

AUTHORS' SUMMARY.

THE HEART IN OLD AGE. FREDRICK A. WILLIUS and HARRY L. SMITH, Am. Heart J. **8**:170, 1932.

This study of the heart comprised 381 patients, ranging in age from 70 to 99 years, who came to necropsy; 59.4 per cent of the patients were between the ages of 70 and 74, whereas 15.7 per cent were 80 years or older. There were five men to one woman. Varying degrees of coronary sclerosis occurred in all cases, but the involvement was moderate to advanced in 72.5 per cent. Likewise, aortic sclerosis was a constant finding, but existed in from moderate to marked degree in 80 per cent of the cases. Sclerosis of the valves occurred in 92.7 per cent. Cardiac disease other than arteriosclerosis was present in 16.4 per cent of the cases. The blood pressure in 371 cases indicated a tendency toward hypertension. The cause of death in this group of aged patients were diverse. Only 12.6 per cent died of heart disease. This clearly shows the suitability of the material for a study of this nature.

AUTHORS' SUMMARY.

MEDIASTINAL ENLARGEMENT IN ACUTE LEUKEMIA. JEAN V. COOK, Am. J. Dis. Child. **44**:1153, 1932.

The cases of nine boys with massive leukemic enlargements of the thymic region are reported. All died of acute leukemia, although clinical evidences of mediastinal tumor were noted in four before the development of a leukemic blood picture. Postmortem examination in two cases revealed large lobular masses in the thymic areas, which microscopically did not present normal thymic elements, but were made up of mononuclear leukemic cells (probably myeloid) held together by connective tissue stroma. Extensive infiltration by similar cells was seen in the liver, kidneys, spleen and other tissues. All lymphoid structures were moderately enlarged and infiltrated with the leukemic cells. A review of eighty-three cases, including the nine not previously reported, shows that the condition affects males almost six times as frequently as females, and that over 90 per cent occurred in persons under 30 years of age. The mediastinal mass is probably the result of leukemic cells carried there by the blood stream rather than a true neoplastic tumor arising in situ.

RALPH FULLER.

CONGENITAL DEFECT OF THE SKIN IN A NEW-BORN INFANT. VERNON BOOTH DOWLER, Am. J. Dis. Child. **44**:1279, 1932.

In consideration of the two lumbar defects, attention is directed to the dimpled "depressions" so often seen in the routine examinations of groups of children of all ages. These so-called "dimples" are usually seen more frequently at the following sites: at the acromion eminences at the shoulder, over the olecranon at the elbows and at the posterior superior iliac spines. The premise is offered at this time that these dimples represent completely healed areas of congenital cutaneous defect. Again, the suggestion is made that, in view of the deep grooving of the defects of the leg, the so-called amniotic grooves that have been noticed not infrequently on the lower extremities of children may be, in reality, totally healed cutaneous defects. It is also evident from a study of this case that the term congenital cutaneous defect should obviously include loss of subcutaneous tissue.

AUTHOR'S SUMMARY.

GLOMERULAR LESIONS ASSOCIATED WITH ENDOCARDITIS. E. T. BELL, Am. J. Path. **8**:639, 1932.

Two forms of glomerulitis, namely, diffuse and embolic, are found in association with endocarditis. Diffuse glomerulitis was found with the various types of endocarditis as follows: acute rheumatic, 22.2 per cent; acute primary bacterial, 28.6 per cent; subacute bacterial, 64.8 per cent, and secondary acute, 33.3 per cent. It is characterized by an increase in the number and size of the endothelial cells and often by thickening of the capillary basement membrane. The extent of capillary obstruction is usually much less than in clinical acute glomerulonephritis, but in seven instances of subacute endocarditis glomerulitis had reached the clinical level. Diffuse glomerulitis bears some relation to the intensity and duration of septicemia. Embolic or focal glomerulitis was found in the different forms of endocarditis as follows: acute rheumatic, 2.9 per cent; acute primary bacterial, 7.1 per cent; subacute, 52.8 per cent, and secondary acute, 5.8 per cent. In one instance there was no endocarditis. Two distinct types of embolic lesions occur, the fresh hyaline and the fibrous. The fresh hyaline lesion in its simplest form is a capillary thrombosis, and all the smaller lesions are readily recognized as such. The larger lesions are composed of many thrombosed capillaries, which may be identified until the capillary walls have undergone necrosis. The hyaline lesion is not an infarct but a thrombosis and necrosis of capillaries resulting from the lodgment of bacteria. The necrotic portion of the glomerulus disintegrates and disappears. The fibrous lesion is a reaction characterized by a marked growth of the basement membranes of the capillaries. The thickened membranes obliterate the capillaries and give the glomerulus a fibrous structure. The fibers are formed entirely from basement membranes; there is no invasion by fibroblasts from without. The fibrous lesion, like the fresh hyaline, may involve one or more lobules or the entire glomerulus. It develops independently of the fresh hyaline lesions. In subacute bacterial endocarditis there were fifteen instances of severe renal insufficiency, of which five were due to embolic glomerulonephritis, seven to acute glomerulonephritis and three to chronic glomerulonephritis. The fresh hyaline embolic lesions develop earlier that the fibrous, and may be found at any time during the course of the disease. The frequent absence of embolic lesions in typical clinical examples of subacute bacterial endocarditis has not been explained. Diffuse glomerulitis is frequently found in association with embolic lesions. Epithelial crescents frequently cause atrophy of the glomerular tufts by compression. Fibers form between the epithelial cells and convert the crescent into a dense fibrous structure. These fibers are of epithelial origin. In the glomeruli, fibers which later give the staining reactions of collagen are formed from three distinct sources: intracapillary fibers from the endothelial cells, fibers formed from thickened capillary basement membranes and fibers formed by the epithelial cells of the crescents.

AUTHOR'S SUMMARY.

GLOMERULAR CHANGES INDUCED BY URANIUM NITRATE, MERCURIC CHLORIDE AND POTASSIUM BICHROMATE. W. C. HUNTER and J. M. ROBERTS, Am. J. Path. **8**:665, 1932.

By a special staining method (azocarmine) distinct changes, interpreted as evidences of injury, can be demonstrated in the glomerular basement membrane of kidneys damaged by uranium nitrate, mercuric chloride and potassium bichromate. The lesions in the basement membrane are purely degenerative in character, are present in both acute and chronic stages of chemical nephropathies and appear to be permanent. The renal glomerulus is more vulnerable to poisons than the tubules, and fails to develop the same degree of increased resistance toward them. The opinion is advanced that alterations in the basement membrane of the type described may play an important rôle in the renal disturbances induced by certain metallic salts. Fibrosis and connective tissue hyperplasia are not responsible for the appearance of the glomeruli in chronic uranium and sublimate nephropathies. The existence of other long recognized glomerular changes demonstrable with ordinary stains is affirmed. Uranium nitrate and mercuric chloride produce more histologic alterations in the glomeruli than potassium bichromate.

AUTHORS' SUMMARY.

CYSTIC NECROSIS OF AORTIC MEDIA. A. R. MORITZ, Am. J. Path. **8**:717, 1932.

Three cases of spontaneous rupture of the aorta with cystic necrosis of the media have been described. The necrosis developed focally in areas that were the seat of chromatropic or mucinous degeneration, and was not associated with any significant intimal change or inflammatory reaction. These cases have been compared with the previously reported cases of this disease, and certain additional observations made. Tearing of the elastic elements occurred with and without cystic change, and neither the cystic change nor the elastic tears were limited to the ascending arch of the aorta. The lesions were qualitatively similar to those commonly seen in sclerotic aortas, and differed in that the necrotic foci were larger and exhibited a greater tendency to repair. In the cases reported to date evidence of hypertension has been common but not constant, and in a considerable number the rupture has occurred while the patients were at rest. Additional studies will be profitable in establishing the similarity or dissimilarity of this disease to the changes commonly seen in arteriosclerosis without advanced intimal lesions.

AUTHOR'S SUMMARY.

COMMON MESENTERY WITH INTESTINAL OBSTRUCTION. A. R. MORITZ, Am. J. Path. **8**:735, 1932.

Four cases of mesenterium commune have been described, one in an infant manifesting no disturbance referable to the anomaly, and three in infants who died of intestinal obstruction secondary to the hypermotility engendered by the defective mesenteric attachments. In two of the infants, the obstruction was caused by a volvulus of 360 degrees in a clockwise direction, which, because of the abnormal motility of the terminal portion of duodenum, reversed not only the plancs of the small and large intestine but also the relation of superior mesenteric artery to the duodenojejunal segment of the intestine. The condition in these two cases was such as to stimulate reversed developmental rotation. These cases illustrate the surgical necessity of determining at the outset whether the condition is a real reversed rotation or a secondary volvulus due to defective fixation. If a correction of a true reversed rotation established during the third month of fetal life is made, one must regard the reversal as normal for that person, while only the volvulus type may be reduced by a return to the normal position.

AUTHOR'S SUMMARY.

FIBROCYSTIC DISEASE OF THE BONES WITH TUMOR OF A PARATHYROID GLAND. R. S. ROSEDALE, Am. J. Path. **8**:745, 1932.

The literature concerning the development of the concept of the relation of generalized fibrocystic disease of bones to hyperparathyroidism has been reviewed. A case of generalized fibrocystic disease of the bones with a tumor of the parathyroid gland has been presented.

AUTHOR'S SUMMARY.

THE STRUCTURE OF THE THYROID IN THE NEW-BORN. V. I. KRINSKAJA. Frankfurt. Ztschr. f. Path. **43**:41, 1932.

Contrary to the results of other research, colloid substances were found frequently in the thyroid in the new-born. In only three of the fifty thyroids examined was colloid missing. Fully developed follicles were regularly present. The author, whose material was taken from Baku, Russia, states that at present she is unable to explain the discrepancies between her findings and those reported by western European investigators.

AUTHOR'S SUMMARY.

TERTIARY SYPHILIS OF THE LIVER IN CHILDREN AND ITS RELATION TO CIRRHOSIS. U. PETERSEN, Frankfurt. Ztschr. f. Path. **43**:44, 1932.

The clinical diagnosis of the condition of a 4 year old girl was syphilitic cirrhosis of the liver. The postmortem diagnosis was lobulated syphilitic liver, enlarged spleen, lipoid nephrosis, ascites and purulent peritonitis. Even though no spirochetes were found in the liver, the diagnosis of lobulated syphilitic liver was made because of the coarse granular appearance, a productive inflammation starting from the capsule and extending into the periportal spaces, while the liver tissue in general was well preserved. Also, the lipoid nephrosis seemed consistent with syphilis. Clinically, there was a typical saddle nose, and the Wassermann reaction was positive when the child was first seen. In reviewing the literature critically, the author did not become convinced of the existence of a true syphilitic cirrhosis.

O. SAPHIR.

DIFFERENTIAL DIAGNOSIS OF GENUINE ATROPHY OF THE LIVER AND ACUTE PHOSPHOROUS POISONING OF THE LIVER. H. KUBO, Frankfurt. Ztschr. f. Path. **43**:56, 1932.

Six cases of acute phosphorus poisoning came under observation, death occurring in from seven hours to five days. The liver of the patient who died seven hours after having taken two tubes of "phosphorus paste" (used for rat poisoning) revealed necrotic foci within the acini without definite appearance of fat in the liver. The same observation was made on rabbit's livers, the rabbits dying from three and one-half to four and one-half hours after having been poisoned with phosphorus paste. Because of the fact that fatty metamorphosis of the liver always is taken as an indication of phosphorus poisoning, in differentiating this condition from genuine (yellow) atrophy of the liver, no significant fat, however, being present in the livers of the patients dying shortly after phosphorus poisoning, the author concludes that no strict differentiation of these two diseases of the liver can be made grossly or histologically.

O. SAPHIR.

A RARE MALFORMATION OF THE CORONARY VESSELS. I. LÖWENHEIM, Frankfurt. Ztschr. f. Path. **43**:63, 1932.

Both coronary arteries originated normally. The first portion of the right coronary artery up to a point about 2 cm. from its mouth was of normal width.

Beginning from there, the lumen of this artery abruptly became much wider, measuring about 6 cm. in circumference. The dilated portion extended up to the region of the septum. At first glance, it seemed as if the dilated portion would end blindly. Close inspection, however, revealed that a small communication existed between the dilated end-portion of the right coronary artery and the right coronary vein. The latter also revealed a normal orifice and first portion. Its distal portion, however, which communicated with the distal portion of the right coronary artery, also was markedly dilated. Microscopically, neither the sections taken from the artery nor those from the vein showed significant changes.

O. SAPHIR.

DIFFUSE SCLEROSIS (LEUKENCEPHALITIS SCLEROTICANS). J. CASPER, Frankfurt. Ztschr. f. Path. **43**:69, 1932.

A 34 year old man, a diabetic patient who four months before admission to the hospital was ill with pneumonia, complained of headache, dizziness, vomiting, changes in the ocular muscles, and right-sided paresis. The cerebrospinal fluid was sterile on bacteriologic examination. The white blood count revealed 15,100 cells. The temperature rose to 39.5 C.; the patient became somnolent, and died six days after admission. The clinical impressions were: possible encephalitis; Schilder's disease, and tumor of the region of the pons (abscess?). Postmortem examination of the brain revealed a large, not well defined area corresponding to the hemisphere of the left occipital lobe, in which there was a marked loss of myelin sheaths combined with a proliferation of glia. A few such foci were also present in the pons. The cortical portion of the brain and the basal ganglia revealed no changes. Nowhere did the proliferation of the glia assume tumorous growth. The capillaries were dilated in the marginal portions of these areas, and some of the vessels were surrounded by round cells. The author believes that the changes in the brain were the result not of bacterial invasion but of bacterial toxins.

O. SAPHIR.

THE GLIA REACTION IN ACUTE INFECTIONS AND INTOXICATIONS AND FOLLOWING ROENTGEN TREATMENT. B. N. MOGILNITZKY and W. S. RJASANOWA, Frankfurt. Ztschr. f. Path. **43**:114, 1932.

The material used for this study was taken from forty-four cases of sepsis, pneumonia, erysipelas, tetanus, diphtheria, scarlet fever, anthrax infections, alcohol and opium poisoning, eclampsia and uremia. In twenty instances, rabbits were exposed to roentgen radiation, and in three instances rats were poisoned with opium. Also, a series of dogs were exposed to roentgen radiation. The author states that in cases of acute infectious diseases and intoxications, and as a result of roentgen treatment, a proliferation of Hortega's elements, and of apolar glia fibers with an increase of the oligodendroglia occurs. In many infectious diseases, the microglia is exposed to destructive changes. No relation could be found between an increase of Hortega's elements and the degree of changes of the ganglion cells. The proliferation of microglia forms the morphologic basis for the so-called encephalopathies and "occult" infections of the brain. The function of astrocytes, Hortega's elements and the apolar glia is discussed.

O. SAPHIR.

RUPTURE OF THE AORTA OF TUBERCULOUS ORIGIN. G. HABÁN, Frankfurt. Ztschr. f. Path. **43**:175, 1932.

A 27 year old man, whose right kidney and both epididymes were removed because of tuberculosis, suffered from hematemesis and marked anemia. The clinical diagnosis was gastric ulcer. He died after an attack of hematemesis. At autopsy, a tuberculous ulcer of the aorta was found, which had perforated into the esophagus. There was miliary tuberculosis of the lungs, spleen, liver and left kidney, in addition to old calcified tuberculosis of the hilus nodes of the lungs

and scars on the apex of the right lung. The author believes that the rupture of the aorta was not the result of the presence of tuberculous granulation tissue in the media, but was caused by necrosis of the media which in turn might have been the result of toxins of the tubercle bacilli or, possibly, of thrombosis of the vasa vasorum.

O. SAPHIR.

THE SPLEEN IN CASES OF ILEUS. T. ROMSAUER, Frankfurt. Ztschr. f. Path. **43**: 184, 1932.

There are no specific changes in the spleen grossly or histologically, from which the presence of an ileus may be inferred. The histologic changes resemble those found in so-called septic spleens.

O. SAPHIR.

CONGENITAL DEFECT OF THE TIBIA. C. ALETTER, Frankfurt. Ztschr. f. Path. **43**: 196, 1932.

The right tibia was missing. The left proximal portion of the left tibia was normal, but its distal portion was abnormally developed. Both patellae were absent. There also were malformations in both ankle joints.

O. SAPHIR.

PATHOGENESIS OF RACHITIS AND CLINICAL OBSERVATIONS. L. LOEFFLER, Frankfurt. Ztschr. f. Path. **43**:231, 1932.

An attempt is made to explain rachitic skeletal changes on the basis of pathologic anatomy and comparative pathology. The author concludes that in rachitis there are a quantitative and a qualitative change in the structure of the bones. The quantitative change is the cause of the qualitative change, the essential of which is the decrease of the calcium content of the bones. The disturbance of the calcium metabolism is secondary. Because of the fact that severe respiratory disturbances, such as bronchiectasis and pneumonia, may be present in patients with rachitis, they should not be overlooked clinically. Sometimes they may be considered the cause of death in patients with rachitis.

O. SAPHIR.

ROUND CELL INFILTRATIONS WITHIN THE SUPRARENALS. J. SOÔS and E. RUSZKÓ, Frankfurt. Ztschr. f. Path. **43**:340, 1932.

Round cell infiltrations were never found in the suprarenal cortex of infants and of young Hungarian pigs. They neither constitute normal findings nor are present congenitally. They may be present in cases of intoxication, of infectious disease and of any diseases which may heal without leaving remnants. Even though they are sometimes found in cases of sudden death, it is more likely that they represent the result of a slowly developing chronic disease within the suprarenals, and, therefore, they should not be brought in correlation with an acute disease. The author believes that small hemorrhages, necrosis of cortical cells or lipoid changes produce a round cell infiltration. The most common location of such round cell infiltrations is the zona reticularis. Their purpose is the carrying away of cellular débris, but they cannot be regarded as blood-forming foci.

O. SAPHIR.

SUPRARENAL HEMORRHAGE. A. KRAUS, Frankfurt. Ztschr. f. Path. **43**:372, 1932.

Hemorrhages of the suprarenals may cause in rare instances a hemorrhage into the loose connective tissue around the kidneys. Perforation of such hemorrhages into the abdominal cavity in the adult is rare in contradistinction to such perforations in the new-born. Repeated hemorrhages into the suprarenals might occasionally form large bloody cysts. Small hemorrhages often constitute an

incidental finding, but larger hemorrhages into both suprarenals are fatal. Clinically, patients suffering from hemorrhages into both suprarenals reveal a pseudoperitonitic complex of symptoms (abdominal pains and rigidity, intestinal spasms, obstipation, and vomiting). Such clinical findings, which are explained at autopsy by hemorrhage into both suprarenals, however, are not common. The pathogenesis of such hemorrhages is not fully understood at the present time. It is possible that the peculiar structure of the suprarenal vein constitutes a factor in the explanation of these hemorrhages.

O. SAPHIR.

PERIARTERITIS NODOSA OF THE KIDNEY. A. HINRICHS, Virchows Arch. f. path. Anat. **280**:51, 1931.

In generalized periarteritis nodosa the kidney is frequently involved. Grossly, the renal involvement presents nothing characteristic; the kidney is usually scarred by areas of healed infarction, or it may be a large red or large white kidney. In the case reported by Hinrichs, the kidneys were especially involved and on the cut surface revealed innumerable small nodules in the cortex and medulla. The nodular character was due to the lesions of periarteritis nodosa. There were no recent or older areas of infarction.

O. T. SCHULTZ.

DISSEMINATED "MEDIONECROSIS" OF THE AORTA. M. CELLINA, Virchows Arch. f. path. Anat. **280**:65, 1931.

A histologic study of a hitherto undescribed form of necrosis of the media of the aorta is presented. Previously recognized forms of necrosis of the media are the idiopathic necrosis associated with spontaneous rupture of the aorta and a mucoid degenerative necrosis which also leads to rupture. The form of necrosis described was encountered in the routine examination of the aortas of elderly persons. This led to a systematic histologic examination of the aortas of ten persons from 71 to 95 years old. The aortas selected were free of calcifying atherosclerosis. Multiple disseminated areas of necrosis were found in every case. The lesions were most numerous in the arch; they were not entirely absent in the thoracic and abdominal aorta. The necroses occurred in the form of streaks from 1 to 10 mm. long that ran parallel to the inner surface of the aorta. They were most numerous in the region of the internal elastic lamella and in the inner third of the media. Characteristic of the areas of necrosis is the complete absence of nuclei and of nuclear remnants in them. A previous increase of elastic and fibrous tissue could be detected in most of the necroses; in a senile atherosclerotic aorta examined for purposes of comparison, the necroses described bore no relation to the atheromatous areas. The cause of the necrosis is not known, but may be a toxic agent that is universally operative in elderly people. In most of the aortas with the disseminated necroses there were seen also minute nonnecrotic areas from which nuclei had disappeared; such areas may be the precursors of the necroses.

O. T. SCHULTZ.

LOCALIZED THICKENINGS AND POCKETS OF THE ENDOCARDIUM. I. M. WERTKIN, Virchows Arch. f. path. Anat. **280**:87, 1931.

The author describes eight hearts with localized, ridgelike areas of thickening of the endocardium and pocket formation. The thickening of the endocardium is brought about by hyperplasia of the inner layer of the endocardium. It is due not to inflammation but to the mechanical impingement of the blood stream against the endocardium. The formation of Zahn's endocardial pockets is secondary to the formation of the area of thickening and is due to the same mechanical factors. The structures discussed are situated most often on the septal surface of the left ventricle, just below the aortic valve. When the opening of the pocket is directed upward, it is usually due to the regurgitating stream of blood in aortic insufficiency. When the opening is directed toward the apex of the ventricle, it is due

to a combination of diastolic backflow and systolic pressure. In two hearts, the unusual localization of the pocket in one case and the unusual form of the pocket in the other could not be explained by any of the accepted theories. The author is also unable to furnish an explanation of the presence of smooth muscle in some of the structures described by him. There is no analogy between the formation of endocardial pockets and of the semilunar valves, and the formation of pockets is not a purposeful functional adaptation. O. T. SCHULTZ.

RING-SHAPED THICKENING OF THE ENDOCARDIUM WITH VALVELIKE POCKETS. K. WOLFF, Virchows Arch. f. path. Anat. **280**:107, 1931.

A heart with vegetative aortic endocarditis, the clinical manifestations during life being those of aortic stenosis, presented a ring-shaped thickening of the endocardium of the upper part of the left ventricular surface of the septum. The area of thickening extended onto the posterior surface of the anterior segment of the mitral valve; except for the thickening, there were no inflammatory or other changes on this surface of the valve. From the ring-shaped area of thickening there had been formed a series of small, valvelike pockets the openings of which were directed toward the apex of the heart. Histologic examination revealed no inflammatory reaction in the structure described. Smooth muscle fibers were seen at the base of the pockets. Wolff ascribes the thickening to mechanical factors, and the formation of the pockets to the action of the systolic pressure in a diastolic backflow. The structure could have no useful function. O. T. SCHULTZ.

TRAUMATIC EPIDERMAL CYSTS. A. BEHRENS, Virchows Arch. f. path. Anat. **280**:145, 1931.

The author presents a brief discussion of traumatic epidermal cysts, which occur usually on the palmar surface of the hand or the flexor surface of the fingers. He describes three such cysts. In one, the trauma led to the formation of secondary cysts from an original misplacement cyst that had been present for many years. In another, the trauma led to fracture of a phalanx and to misplacement of epithelium into the bone, where the cyst developed. In the third, the cyst developed in close proximity to the terminal phalanx and led to pressure atrophy and disappearance of bone. O. T. SCHULTZ.

LOCALIZED GLIOSIS OF THE MEDULLA. G. POMMER, Virchows Arch. f. path. Anat. **280**:205, 1931.

In a man who for six years before death had been afflicted with paralysis of the left upper and lower extremities, paralysis of the right side of the face and anesthesia in the distribution of the third branch of the left fifth nerve, microscopic examination of the brain stem revealed a sharply circumscribed area of gliosis that had replaced the tissues of the region of the right olivary body. In a less sharply defined manner the area extended upward and involved the nuclei of the sixth and seventh nerves and the fiber tract of the fifth nerve of the right side. The lesion resulted from vascular obliteration. O. T. SCHULTZ.

PROSOPOTHORACOPAGUS. O. WALBAUM, Virchows Arch. f. path. Anat. **280**:275, 1931.

The monstrosity described is compared with previously reported similar ones and with six thoracopagi studied by the author. The main feature that distinguishes double monsters with fusion of both face and thorax from those with fusion of the thorax alone is the single pharynx, esophagus and stomach of the former. O. T. SCHULTZ.

CONGENITAL DIVERTICULUM OF THE CECUM. B. ODQVIST and T. PETRÉN, Virchows Arch. f. path. Anat. **280**:581, 1931.

After a brief discussion of some of the more unusual forms of congenital diverticulum of the intestine, the authors present a description of a diverticulum of the cecum that was observed by chance during necropsy on a 3 year old girl. A typical Meckel's diverticulum was situated 90 cm. above the ileocecal valve. The appendix was given off from the cecum in the normal position. Arising in the angle formed by the junction of the ileum with the large bowel was a blind diverticulum 6 cm. long by 2.5 to 3 cm. in diameter. It possessed a mesentery in common with the appendix. Its lumen communicated with that of the intestine. Its wall was composed of a mucosa, submucosa, inner muscular coat and external muscular coat. The authors do not consider the structure a reduplicated appendix or a bifurcated cecum, but a congenital diverticulum of the cecum.

O. T. SCHULTZ.

HISTOPATHOLOGY OF THE INTESTINE IN ANKYLOSTOMIASIS. W. ROTTER, Virchows Arch. f. path. Anat. **280**:587, 1931.

This work comes from Costa Rica. The usually described acute lesions of ankylostomiasis are small areas of hemorrhage in the submucosa of the upper part of the small intestine, beneath the depths of the folds of the mucosa, where the worms have attached themselves by their hooklets. The traumatic hemorrhage is followed by necrosis and leukocytic infiltration, due to toxic action. In healing, these lesions are transformed into localized fibrous plaques that contain hemosiderin. There occur also minute hemorrhages limited to the mucosa and leukocytic infiltration limited to the stroma of a few villi. These reactions are due to the toxic action of the parasite. As a chronic lesion, the author describes diffuse fibrosis and thickening of the submucosa, over which the mucosa may be fairly normal but is more often thin and atrophic. It is to these chronic lesions that the author ascribes the persisting anemia and cachexia of the infestation.

O. T. SCHULTZ.

A CASE OF APLASIA OF THE CEREBELLUM. N. K. LYSSENKOW, Virchows Arch. f. path. Anat. **280**:611, 1931.

Because of the rarity of cerebellar aplasia in adults this gross and microscopic study of the brain is presented, although the clinical history and a protocol of the necropsy could not be found. It is known only that the specimen was from a man who reached the age of 25 years, that he was said to have been psychically normal, and that he had never walked. The vermis of the cerebellum and all its structures were absent. The lateral lobes were much smaller than is normal. They revealed the normal topography, but all the structural elements were quantitatively greatly reduced. The nuclei and tracts of the brain stem that have no direct connection with the cerebellum were normal.

O. T. SCHULTZ.

VASCULAR CHANGES IN CHRONIC LIGNEOUS THYROIDITIS (RIEDEL'S STRUMA). F. ROULET, Virchows Arch. f. path. Anat. **280**:640, 1931.

In three thyroids that were the seat of the chronic inflammatory process usually associated with Riedel's name, the author describes vascular changes much more marked than have hitherto been noted. The process involved chiefly the smaller and terminal veins; in one case the small arterioles were also involved. The original tissue elements of the wall of the vein were separated by a cellular granulation tissue that penetrated the wall from the adventitia. The infiltrating tissue was rich in plasma cells. The tissue may penetrate the intima and grow

into and occlude the lumen without thrombosis. Disappearance of plasma cells and lymphocytes and collagenous transformation of the stroma may transform the vessel into a nodule the original vascular character of which is not recognizable. The vascular lesion is suggestive of syphilis, but the author does not consider the process syphilitic.

O. T. SCHULTZ.

DEVELOPMENT ANOMALIES ASSOCIATED WITH ABSENCE OF THE CAUDAL END OF THE VERTEBRAL COLUMN. A. FELLER and H. STERNBERG, Virchows Arch. f. path. Anat. **280**:649, 1931.

The authors give a detailed account of the conditions found in two monstrosities of the sympus apus type and compare them with the conditions found in two other monstrosities with maldevelopment of the lower extremities. Maldevelopments associated with defects of the lower end of the vertebral canal they classify as monopus, sirenoid monopus and siren. The term monopus they would reserve for the anomaly in which the vertebral defect is asymmetrical and involves one side only, leading to the failure of development of one posterior limb. Sirenoid monopus they would apply to the monstrosity in which the asymmetrical defect involves also the midportion of the lower vertebral column. Siren is applied to the anomaly associated with a median and bilaterally symmetrical vertebral defect. The absence of the allantois and of one umbilical artery in sirens indicates the very early stage of embryonic development during which the maldevelopment arises. The latter is not due to fusion of two limbs or regression of one limb bud or to external factors, but is due to factors inherent in the germ plasm which result in the lack of formation of sufficient tissue for two limb buds.

O. T. SCHULTZ.

PLICATION OF DIAPHRAGMATIC PLEURA WITH ABNORMAL LOBATION OF LUNG. H. TESSERAUX, Virchows Arch. f. path. Anat. **280**:693, 1931.

The anomaly described occurred in a 7 month old boy who died of sepsis of otitic origin. The right pleural cavity was incompletely divided into two portions by a fold of the diaphragmatic pleura that grew upward along the vertebral column, and that divided the lower lobe of the lung into a smaller posterior lobe and a larger anterior portion. A normal middle lobe had not been formed. This unusual anomaly, of which the author could find only three previously reported examples, was ascribed by H. Eppinger, who reported the first case in 1902, to abnormality in the course of diaphragmatic vessels. Tesseraux holds that the anomaly is due to maldevelopment of the embryonic pleuroperitoneal membrane. In the four cases thus far described, the anomaly has been on the right side.

O. T. SCHULTZ.

FUSED DOUBLE MONSTROSITIES AMONG MAMMALS. ELSBET ENGEL, Virchows Arch. f. path. Anat. **280**:706, 1931.

Six cephalothoracopagi are pictured and described. These were distributed among four species as follows; hog, two; rabbit, two; dog, one, and lamb, one.

O. T. SCHULTZ.

CEREBRAL INJURY IN NEW-BORN CHILDREN CONSEQUENT ON BIRTH TRAUMA; WITH AN INQUIRY INTO THE NORMAL AND PATHOLOGIC ANATOMY OF THE NEUROGLIA. ERIK RYDBERG, Acta path. et microbiol. Scandinav., 1932, supp. 10, p. 1.

In the human fetus the glia to a large extent forms a syncytium. The evidence points to its ectodermal origin. In the new-born fatty substances accumulate normally about glia cells and their expansions. These fatty substances may form

material for the myelinization of nerve fibers. The regressive changes in the glia and nerve fibers in injuries to the brain in the new-born are essentially of the same nature as those that occur in injuries to the brain later in life. The nerve fibers are more resistant than the fetal glia, which readily undergoes softening. Phagocytic fat granule cells may come from different sources. That intracranial hemorrhages in the new-born so frequently are multiple indicates that they are due to general disturbances of the intracranial circulation in the course of birth, but local vascular injuries may occur also as in tentorial tears. In seventy-five new-born infants, gross intracranial hemorrhage, by far most commonly meningeal, occurred in fifty-eight; hemorrhage into the brain tissue or ventricles was found in twenty-eight of the seventy-five cases. Subependymal hemorrhages are characteristic of premature fetuses. Microscopic capillary hemorrhages are almost constant in the new-born. In thirty-four new-born infants with major cerebral symptoms, considerable intracranial hemorrhage accompanied by softening was found in all except six cases in which degenerative changes were present. Cases of brain trauma in birth may run their course without symptoms. Account is given of necropsies in forty-eight instances in which there were major cerebral symptoms during the first few days of life followed by survival for one year or longer. Only nine of these infants could be grouped as normal; one-third were classed as idiots or imbeciles; the mentally retarded numbered ten, and there were nineteen epileptic infants. In the chapter on treatment the value of the injection of blood (universal donor) into the superior longitudinal sinus is emphasized.

AUTHOR'S SUMMARY.

Microbiology and Parasitology

BEHAVIOR OF BACTERIOPHAGE IN BODY FLUIDS AND IN EXUDATES. M. G. COLVIN, J. Infect. Dis. **51**:527, 1932.

There is a nonspecific inhibitory effect of serum on bacteriophagy, which was first observed and reported by Gratia. This phenomenon associated with the lysis of staphylococci has been shown in connection with other organisms by subsequent investigators. In this report, the results of further investigations in regard to the importance of the various factors concerned in inhibition of bacteriophagy in body fluids are outlined. It has been found that variation of serum, body fluid, race of bacteriophage and bacterial strain or species introduces distinct differences in the amount of inhibition. Attempts to adapt a staphylococcic or a streptococcic phage to produce complete lysis in serum have been practically unsuccessful. It is shown that repeated contact with serum may have a tendency to make an organism lysis-resistant, and consequently an adaptation to resist lysis develops. A study of the mechanisms of inhibition to lysis shows that serum delays multiplication of the bacteriophage, but does not prevent specific fixation of the corpuscle. In the serum, the protein fraction is the main factor in inhibition of lysis, while in urine the crystalloid fraction inhibits. The observations suggest that bacteriophagy in the body is much modified as compared with test tube standards of lysis. This modification is in the direction of lessening the sterilizing capacity of the bacteriophage.

AUTHOR'S SUMMARY.

LÖWENSTEIN'S CULTURE METHOD FOR TUBERCLE BACILLI. W. HAYMAKER, W. EKHART and J. FREUND, J. Infect. Dis. **51**:562, 1932.

With Löwenstein's method, no growth of tubercle bacilli was obtained from thirty-eight samples of blood from tuberculous patients. In four cases of polyarthritis, three of rheumatic heart disease and one of chorea, no tubercle bacilli were found in the blood, either by the cultural method or by inoculation of guinea-pigs.

AUTHORS' SUMMARY.

BACTERIA CAUSING ACUTE CORYZA. L. HOYLE, J. Path. & Bact. **35**:817, 1932.

The results of extensive observation of the relation between appearances of Bacillus influenzae and pneumococci in the upper respiratory tract and the occurrence of attacks of acute coryza suggest that many of the more severe attacks of coryza may represent infections by these organisms.

AUTHOR'S SUMMARY.

THE FILTRATION OF HERPES VIRUS THROUGH GRADED COLLODION MEMBRANES. W. J. ELFORD, J. R. PERDRAU and W. SMITH, J. Path. & Bact. **36**:49, 1933.

The size of the virus of herpes has been estimated to be from 0.1 to 0.15 microns by filtration experiments in which both cerebral and testicular strains of the virus were studied.

AUTHORS' SUMMARY.

PULMONARY TUBERCULOSIS WITH THE BOVINE TYPE OF THE BACILLUS IN THE SPUTUM. W. M. CUMMING, W. M. FOSTER and A. S. GRIFFITH, J. Path. & Bact. **36**:153, 1933.

The methods of the isolation and identification of tubercle bacilli of the bovine type from fourteen cases of pulmonary tuberculosis in England are described. The distribution of the cases is as follows: From 211 unselected cases of pulmonary tuberculosis in a northern urban industrial population (Bradford), six bovine strains were isolated. In five of these cases there had previously been a glandular lesion. Of fifty-one cases of pulmonary tuberculosis in the north of England (including the Bradford cases) in which there had been definite evidence of a previous glandular lesion, ten have been shown to be due to the bovine type of the bacillus. Of fourteen similar cases in the south, one has been shown to be due to the bovine type. Of fifty-nine cases of pulmonary tuberculosis in the north of England occurring in children under 16 years of age, one has been shown to be due to the bovine type. Of fifty-two similar cases in the south, two have been shown to be due to the bovine type. Of eleven cases of pulmonary tuberculosis occurring in patients coming much in contact with cattle, two have been shown to be due to the bovine type. In any given case of pulmonary tuberculosis, the presence of tubercle bacilli of the bovine type seems to be of definitely unfavorable prognostic significance. It is pointed out that the possibility of the occurrence of man-to-man and of man-to-cow infection with the bovine type of the tubercle bacillus becomes increasingly more difficult to ignore. At autopsy in two of the cases, it was established that the route of infection was alimentary and that the pulmonary lesion was indistinguishable from that due to the human type.

AUTHORS' SUMMARY.

TUBERCULOUS DISEASE IN CHILDREN: ITS PATHOLOGY AND BACTERIOLOGY. JOHN W. S. BLACKLOEK, Special Report Series, No. 172, Medical Research Council, July, 1932.

In 1,800 autopsies on infants and children from a few hours old up to 13 years of age, Blackloek found gross evidence of tuberculosis in 283 (15.7 per cent). In 173 (61.1 per cent) of these the condition was considered due to primary infection of the lungs or of the thoracic lymphatics. The primary pulmonary lesion first described by Parrot, consisting of a localized patch of tuberculous bronchopneumonia which showed a tendency to heal, usually single and subpleural, was found in 148 of 173 cases in which the first site of infection was considered to be thoracic. These primary lesions were found most often in the right lung, the right upper lobe being most frequently involved. The apex of the upper lobe was seldom the seat of a lesion. The tracheobronchial glands in direct anatomic relation to these foci were always diseased. The lesions in the primary focus and related lymph glands were of the same age or that in the glands was more recent, so that a lymphogenous origin of the pulmonary focus seemed unlikely. No retrograde

spread from the tuberculous tracheobronchial glands back into the substance of the lung was observed. None of the primary foci could be shown to have a vascular origin; it is held that these primary pulmonary foci are aerogenic in origin. From the cases in which the primary lesion was found in the lung only the human type of bacilli were obtained, either from the lesion itself or from the regional glands. In 101 cases (35.7 per cent) of tuberculous lesions, the evidence was in favor of an abdominal site of the first infection. Of these, 18—all children under 5 years of age—showed intestinal ulceration, chiefly in the lower end of the ileum. All the children under 1 year of age with intestinal ulcers had been fed on cow's milk. In 83 cases, no ulcers were noted, but the mesenteric glands, chiefly in relation to the lower end of the ileum, were the seat of tuberculosis. The greatest number of primary abdominal lesions were found in the second year of life, that is, at a period when children were consuming large amounts of raw milk. Primary abdominal tuberculosis was less frequent than primary thoracic tuberculosis throughout all ages. There were fewer secondary lesions and less extensive glandular involvement in the cases with primary abdominal lesions than in these with primary thoracic lesions. From these abdominal lesions, 12 human and 54 bovine strains were isolated.

LUKE W. HUNT.

A CARBOHYDRATE COMMON TO THE GROUP OF ACID-FAST ORGANISMS, INCLUDING THE TUBERCLE BACILLI. ARNOLD BRANCH, Tubercle **13**:481, 1932.

Antiserums prepared in rabbits by the inoculation of whole bacterial vaccines of acid-fast organisms give a strong precipitin reaction with a carbohydrate isolated from filtrates of these organisms. This carbohydrate is common to a representative group of the acid-fast organisms, as determined by precipitin tests and passive anaphylaxis in guinea-pigs. The carbohydrate is not related to the pathogenicity or virulence of acid-fast bacilli, as it is present in the saprophytic Mycobacterium phlei and in avirulent strains of bovine (B C G) and avian (A1 [3]) tubercle bacilli. In order to produce specific antiserums for members of the acid-fast group of bacteria, it will be necessary to use antigenic fractions (protein or lipoid). The author used in these tests the human tubercle bacilli, H 37 and a strain from Cobbett; the bovine tubercle bacilli, B 1 (Saranac Lake), B 2 (Parker of Boston) and B C G; the avian tubercle bacilli, A 1 (Saranac Lake); two dissociates; two virulent strains (from Medlar and Schulz); three avirulent strains (porcine 81, Raw-Calmette and Raw Koch from Griffith); a timothy bacillus (from Lister Institute); Mycobacterium thannopheus (Aronson); Mycobacterium marinum (Aronson), and other acid-fast bacilli.

H. J. CORPER.

A LEPTOTHRIX PATHOGENIC FOR MAN (LEPTOTHRIX PLEURITICA). J. L. NICOD, Ann. d'anat. path. **9**:477, 1932.

A pulmonary lesion is described which was due to Leptothrix pleuritica. The lesion was a diffuse chronic granuloma. The organism resembles actinomyces, but differs in its staining reactions, its cultural characteristics and in the kind of granuloma that it produces, although the latter is not specific. It is believed that many atypical cases of actinomycosis are perhaps due to Leptothrix pleuritica.

PERRY J. MELNICK.

CONGENITAL TUBERCULOSIS BY ASPIRATION OF AMNIOTIC FLUID. GEORGES GANDU, Ann. d'anat. path. **9**:891, 1932.

The author discusses the portals of entry of the tubercle bacillus in congenital tuberculosis, and reports a case in which the infection resulted from aspiration of infected amniotic fluid in utero.

PERRY J. MELNICK.

THREE FIRST CASES OF RECURRENT FEVER OBSERVED IN TUNIS. C. NICOLLE, C. ANDERSON and J. LAIGRET, Arch. Inst. Pasteur de Tunis **21**:43, 1932.

The spirochetosis described as Spanish-African recurrent fever was recognized in Tunis. The organisms appeared to be carried by a tick, Ornithodorus erraticus, and to belong to the Spirochaeta hispanica (Buen) group, highly pathogenic for guinea-pigs. In common with other spirochetes of Tunis, the organisms seemed to be indifferent to the species of tick, in which the nymph and adult stages were infected, although the nymph stage was responsible for transfer. Lytic tests with the serum of infected animals indicated a marked specificity among the spirochetes of this group. Cross-immunity tests gave similar indications of specificity. "There are not, in the spirochetes of recurrent fever, species but individuals which one may arrange in groups, characterized by a common pathogenicity and by a common agent of natural transmission."

M. S. MARSHALL.

STATUS OF THE FIXED VIRUS OF RABIES. L. BALOZET, Arch. Inst. Pasteur de Tunis **21**:130, 1932.

The evolution of the fixed Pasteur virus in Tunis shows a more or less coincidental reduction in the period of incubation, an increase in neurotropic properties, and a considerable increase in sensitivity to physical and chemical agents. The Tunis strain has the shortest period of incubation so far as known of any descendants of the Pasteur virus, viz., five and three-fourths days. After three days' drying, it is no longer virulent. In the active state, however, it will infect by eye and often following subcutaneous injection. The evolution of the substrains of the original virus held in different institutes has not been identical.

M. S. MARSHALL.

TRANSITORY TUBERCULOUS BACTERIURIA WITH NEGATIVE TUBERCULIN SKIN TESTS. E. RAMEL, Arch. internat. de méd. expér. **7**:633, 1932.

A case is presented of an 8 year old child, healthy and clinically nontuberculous, who reacted negatively to the tuberculin skin tests but whose urine on two occasions was found to contain typical acid-fast bacilli, proved to be tubercle bacilli by inoculation in the guinea-pig. The syndrome is called transitory tuberculous bacteriuria. The authors present this case as one which is not explicable on the grounds of present theories of humoral antibodies.

RALPH FULLER.

MORPHOLOGIC STUDY OF THE VIRUS OF RABIES. M. C. LEVADITI, R. SCHOEN and M. J-G. MEZGER, Arch. internat. de méd. expér. **7**:655, 1932.

In mice, rats and monkeys inoculated with the street virus of rabies, it is possible to follow the changes in the germ of rabies within the neuron and to understand some of the intermediate phases in the development of the parasite, the protozoan character of which seems more and more probable.

RALPH FULLER.

POSTMORTEM OBSERVATIONS IN SYPHILITIC PATIENTS. G. GULDBERG, Arch. f. Dermat. u. Syph. **166**:730, 1932.

In patients with positive Wassermann tests, but without any other signs of syphilis, microscopic examination from four to fifteen years after the infection showed small specific cellular infiltrations in the aorta, in part with spirochetes, in the para-aortic tissue and in the fibrous tissue of the mediastinum. The inguinal, iliolumbal and mesenteric lymph nodes in these cases showed microscopically a chronic specific lymphadenitis, and in some of them spirochetes could be demon-

strated. These syphilitic foci with spirochetes may be the source of syphilitic processes in the vascular or nervous system, skin or viscera which develop many years after the infection.

AUTHOR'S SUMMARY.

ISOLATION OF TUBERCLE BACILLI FROM THE BLOOD IN TUBERCULOSIS OF THE BONES ACCORDING TO LÖWENSTEIN'S METHOD. A. URGOITI, Beitr. z. klin. d. Tuberk. **80**:480, 1932.

Sixty-seven patients with tuberculosis of the bones and thirty-nine controls were examined. No cultures were obtained from the controls. Twenty-six of the sixty-seven tuberculous patients yielded cultures. These studies were done in Löwenstein's laboratory.

MAX PINNER.

CULTIVATION OF THE TUBERCLE BACILLUS FROM THE BLOOD OF LÖWENSTEIN'S METHOD. H. J. TIEDEMANN, Beitr. z. Klin. d. Tuberk. **81**:450, 1932.

Blood cultures were made by Löwenstein's method in fifteen cases of acute polyarthritis. Although Löwenstein has reported positive results in almost 100 per cent of cases, in no case in this series was it possible to obtain growth of tubercle bacilli. Similar cultures made in fifteen instances of tuberculosis of the skin, ten of tuberculosis of the eye and four of schizophrenia were likewise consistently negative. In only two of fifty cases of far advanced, active, open pulmonary tuberculosis were tubercle bacilli demonstrable in the blood. In three other instances acid-fast rods were demonstrated either macroscopically or microscopically which were apparently not pathogens. That the method is essentially sound was demonstrated by the recovery of tubercle bacilli both from mixtures of normal blood and various amounts of bacilli in vitro and from the blood streams of animals experimentally infected, both subcutaneously and intravenously. The inconstancy with which the latter was achieved, however, suggests that invasion of the blood stream by the tubercle bacillus is not a frequent, nor as yet a fully elucidated, phenomenon.

AARON EDWIN MARGULIS.

BACTERIOLOGIC AND HISTOLOGIC RESEARCHES ON TUBERCLE BACILLEMIA. K. BROCK, Beitr. z. Klin. d. Tuberk. **81**:543, 1932.

The inconstancy and the rarity with which tubercle bacilli may be recovered by Löwenstein's method from the blood stream in cases of tuberclosis, and the lack of correlation with bacteriologic and histologic evidence of focalization in the spleen and the bone marrow, suggest that tubercle bacillemia is not regularly present in tuberculosis, and that when invasion of the blood does occur focalization in the bone marrow and spleen is not invariable.

AARON EDWIN MARGULIS.

MILIARY NECROSES IN THE NEW-BORN INFANT. W. IFF, Beitr. z. path. Anat. u. z. allg. Path. **86**:83, 1931.

Miliary necroses in the new-born infant occur in the liver, spleen, lungs and thyroid and are morphologically unlike any known granulomatous lesions.

Gram-positive short bacilli are occasionally found in these necrotic areas and may be the cause, since pure cultures injected into animals produce similar lesions. Entry is either placental or by vaginal aspiration.

W. S. BOIKAN.

ISOLATED ACTINOMYCOSIS OF THE KIDNEY. J. RAČIĆ, Beitr. z. path. Anat. u. z. allg. Path. **87**:474, 1931.

The author describes a case of long-standing renal pelvic stone, complicated by isolated actinomycotic pyelonephrosis. The patient recovered completely after opera-

tion. The author holds that actinomycosis can form a primary small encapsulated focus in the oral, gastro-intestinal (appendix) or respiratory tract from which an isolated active metastasis to a single organ—for instance, the kidney—can take place.

W. S. Boikan.

Pathologic-Anatomic Diagnosis of Yellow Fever in Monkeys. E. P. Snijders and J. E. Dinger, Virchows Arch. f. path. Anat. **280**:444, 1931.

Seventy-six rhesus monkeys were given injections of yellow fever virus from various sources. This was done not without danger, for one of the authors (J. E. D.) contracted a mild case of the disease following a scratch from one of the monkeys. The course of the disease is short in these animals. Icterus and petechial hemorrhages were variable. Anatomically, the most characteristic lesions were in the liver. These included fatty degeneration and necrosis of the liver cells and the highly characteristic Torres intranuclear inclusion bodies. The latter are considered to be products of nuclear degeneration and have no relation to the virus. Their number has no relation to the virulence. The blood was found to be the most virulent in reproducing the disease. Noguchi's spirochetes could not be demonstrated in Levaditi stains.

Perry J. Melnick.

Some Unusual Manifestations of Echinococcus Disease. H. Schmieta, Virchows Arch. f. path. Anat. **285**:650, 1932.

The author describes four somewhat unusual cases of human echinococcus disease. One was an alveolar echinococcus of the liver that had invaded the walls of the inferior vena cava and portal vein, causing great fibrous thickening of the walls of the vessels. One was a cystic echinococcus of the liver with marked deposition of hematoidin in the cyst. This phenomenon is rare in the cystic form of the disease, but is so common in the multilocular form as to be considered of diagnostic value in differentiating the two forms. The third case was one of primary cystic echinococcus of the spleen with multiple secondary cysts of the same organ, simulating grossly the alveolar form. The final case was one of cystic echinococcus of the mammary gland.

O. T. Schultz.

Multiple Multilocular Echinococcus Disease. G. H. Bartsch and A. Posselt, Virchows Arch. f. path. Anat. **285**:665, 1932.

Multilocular echinococcus occurs most frequently in the liver, and multiple involvement is rare. In the case described by the authors, that of a man, aged 44, the disease of the liver had spread by direct continuity to the diaphragm, lower lobe of the right lung, right suprarenal, right kidney and local lymph nodes. There was metastatic involvement of the spleen, the upper lobe of the right lung and both cerebral hemispheres. The sequence of events could not be determined. Hooklets and heads were found only in the lesions of the brain.

O. T. Schultz.

Double Anthrax Infection. L. Galvan, Virchows Arch. f. path. Anat. **285**:686, 1932.

A 70 year old man who died of anthrax had a lesion of the dorsum of the hand and multiple small recent ulcers of the stomach that contained the bacilli. Both the cutaneous and the gastric lesions were believed to have been primary.

O. T. Schultz.

PARALYTIC DEMENTIA AND SYPHILITIC AORTITIS. H.-J. SCHERER, Virchows Arch. f. path. Anat. **286**:183, 1932.

A number of recent writers have claimed that syphilitic aortitis is less frequent or runs a more benign course in persons with paralytic dementia than in those with nonparalytic syphilis. Scherer's investigation of this problem was based on the necropsy protocols and material of 202 cases of paralytica dementia. Syphilitic aortitis of varying grade was present in 125 of these. This group was compared with 125 cases of syphilitic aortitis in persons with nonparalytic syphilis. Scherer also studied 14 cases of juvenile paralysis and 19 of tables without paralysis. He could find no difference in the incidence of aortitis in the paralytic and in the nonparalytic groups. The subjective and objective clinical manifestations of aortitis were less frequent or less severe in the paralytic group. Aortitis and its sequels were a more frequent cause of death in the nonparalytic group; this was due to a lesser frequency of aortic insufficiency, aneurysm and other severe sequels of aortitis in the paralytic group. Cardiac hypertrophy was less evident in the paralytic group with aortitis; in the latter, the heart was more apt to be atrophic and flabby, as is the rule in paralysis. The most advanced forms of aortitis were anatomically no different in the two groups, but the localization of the process in the milder forms was atypical in the paralytic group. Analysis of the factors that might explain the differences that were found to exist brought to light the fact that the average age at death in the paralytic group was lower than that in the nonparalytic group, and that in the paralytic group without aortitis it was still lower. The severe forms of aortitis in the paralytic group not to be distinguished anatomically from the severe forms in nonparalytic syphilis, occurred in those persons who had reached an age equal to that in the nonparalytic group with advanced aortitis. No histologic differences in the aortitis of the two groups could be detected. The marasmus and enforced idleness of the persons with paralysis may be factors in the lesser degree of aortic and secondary cardiac involvement in this paralytic group. Whether marasmus exerts an influence through its effect on metabolism could not be determined. The author could find no reason to believe that the febrile therapy used in the treatment of paralytic dementia has any effect on syphilitic aortitis. In the 14 cases of juvenile paralysis there was one case of aortitis: the only conclusions drawn are that syphilitic aortitis does occur in juvenile paralysis, and that it is much less frequent than in the paralytic dementia of acquired syphilis. There is as yet not sufficient proof to substantiate the view, postulated by some, that there is a biologic antagonism between neurosyphilis and aortic syphilis.

O. T. SCHULTZ.

CULTIVATION OF TUBERCLE BACILLI FROM THE BLOOD STREAM. H. POPPER, F. BODART and W. SCHINDLER, Virchows Arch. f. path. Anat. **286**:615, 1932.

In a previous communication, the authors reported the results obtained by them with the Löwenstein method for the cultivation of tubercle bacilli as applied to blood obtained from the heart at necropsy. The present report presents the results of the use of this procedure in more than 1,000 examinations. The series includes the previously reported, and some additional, cultivations of blood obtained at necropsy. Positive cultures with macroscopic viable colonies were obtained in a high percentage of cases of miliary and other forms of active tuberculosis. Tissues obtained at biopsy and necropsy, exudates, urine and other similar materials also yielded a high percentage of positive cultures. In the postmortem examination of such materials and of the blood, the cultural method may replace animal inoculation. The negative results of the first 400 cultures of the blood stream were discarded because the Löwenstein technic had not been exactly followed. In the next 435 cultures of the blood during life, no macroscopic growth of tubercle bacilli was obtained. But microscopic examination revealed the presence of acid-fast and alcohol-fast rods in 11.5 per cent of the total. Microscopically positive results were obtained in 42.7 per cent of 7 cases of miliary tuberculosis and in

16.6 per cent of cases of advanced pulmonary tuberculosis. Löwenstein had claimed positive results in a relatively high percentage of cases of rheumatic fever and its complications or sequelae. In cases of this group, the present writers had 21 per cent of microscopically positive results in 38 cases of acute rheumatic fever, in 28.6 per cent of 7 cases of primary chronic polyarthritis, in 16.2 per cent of 6 cases of chorea minor and in 22.1 per cent of 9 cases of endocarditis of rheumatic origin. Five cases of multiple sclerosis, in cases of which Löwenstein had reported a high percentage of positive results, 4 of lymphogranulomatosis, in cases of which several investigators have recently again reported the presence of acid-fast bacilli, and 5 of mycosis fungoides yielded negative results. Positive results were obtained in 9.5 per cent of 21 cases of sepsis and in 6.8 per cent of 44 control cases. The acid-fast rods seen only microscopically in cultures of the circulating blood could not be made to grow when transplanted, except in one instance. This was a case of recurrent rheumatic endocarditis, in which the blood culture yielded a culturally and morphologically characteristic tubercle bacillus that produced typical lesions when inoculated into animals. Twelve strains of acid-fast and alcohol-fast bacilli that could be cultivated proved to be avirulent and culturally unlike the tubercle bacillus. The relatively high percentage of microscopically positive cultures of the blood stream in known cases of tuberculosis indicates that the procedure has value. But similar results in the rheumatic group of diseases indicates that such positive results must be interpreted with care until the relationship of acid-fast bacilli to these diseases is established.

O. T. SCHULTZ.

GENERAL ACTINOMYCOSIS. K. FELLINGER and G. SALZER, Virchows Arch. f. path. Anat. **286**:638, 1932.

The subject was a man, aged 59. The primary site of the disease was the lung. Invasion of the blood stream led to widespread generalization of the process, with meningitis and multiple actinomycotic lesions in the liver, spleen, kidneys, thyroid and thoracic vertebrae. The organism was cultivated at necropsy from the purulent lesions, the splenic pulp, and blood from the heart. The granulation tissue contained many giant cells.

O. T. SCHULTZ.

MYCOSIS FUNGOIDES IN A DOG. D. WIRTH and R. BAUMANN, Virchows Arch. f. path. Anat. **286**:651, 1932.

Multiple nodular lesions of the skin and internal organs consisted of pleomorphic granulation tissue identical with that of human mycosis fungoides. The tissue contained acid-fast bacilli similar to those described by Busny in mycosis fungoides.

O. T. SCHULTZ.

INFECTIOUS MYXOMATOSIS OF RABBITS. E. HAAGEN, Zentralbl. f. Bakt. (Abt. 1) **121**:1, 1931.

The virus of infectious myxomatosis of rabbits was carried in tissue culture through thirty passages with retention of its virulence. The virus in rabbits at the height of infection was present in the erythrocytes, leukocytes, serum, plasma, lungs, kidneys, lymph nodes, spleen, testes, liver and tears. The lungs, lymph nodes and spleen seemed to be the most infectious.

Cell changes, particularly nuclear inclusions, were found not only in the myxomatous tissue but also in the cornea and in the eyelids. These changes are not uniform; they differ in size, structure and staining and should not be identified with the virus, but should be considered merely as products of a reaction of the cells against the virus.

PAUL R. CANNON.

Immunology

STREPTOCOCCIC AGGLUTINATION IN CHRONIC ARTHRITIS AND ACUTE RHEUMATIC FEVER. B. J. CLAWSON, MACNIDER WETHERBY, E. H. HILBERT and H. E. HILLEBOE, Am. J. M. Sc. **184**:758, 1932.

Streptococcic agglutination titers were determined in patients with chronic arthritis and acute rheumatic fever for two strains of streptococci. The first strain was isolated from a patient with acute rheumatic fever and the second from a patient with chronic arthritis. The agglutination titers of patients with these conditions were compared with those of normal persons and of patients with scarlet fever and glomerulonephritis. With the rheumatic strain the agglutination titers in acute rheumatic conditions were higher than normal, while those in chronic arthritis were not. With the chronic arthritic strain the titers were higher than normal in both chronic arthritis and acute rheumatic fever, but higher in the latter. With both strains the titers were decidedly higher than normal in both scarlet fever and glomerulonephritis. In all tests, including those with normal serums, the chronic arthritic strain was agglutinated in higher dilutions than the acute rheumatic strain. The chronic arthritic strain appeared to be more sensitive to agglutination. These findings suggest that both chronic arthritis and acute rheumatic fever are streptococcic infections. The view that chronic arthritis is due to a specific strain is not supported, since the chronic arthritic strain was agglutinated in higher dilutions with serums of patients with acute rheumatic fever than with the serums of patients with chronic arthritis. The lack of strain specificity is also shown by the fact that both the rheumatic and the arthritic strains were agglutinated in higher dilutions with serums of patients with scarlet fever and glomerulonephritis than with the serums of patients with acute rheumatic fever and chronic arthritis.

AUTHORS' SUMMARY.

HISTOLOGICAL STUDIES OF HYPERSENSITIVE REACTIONS. L. DIENES and T. B. MALLORY, Am. J. Path. **8**:689, 1932.

The tuberculin type of hypersensitiveness represents the first stage of the immune response to parenterally introduced protein antigen. It occurs in uninfected as well as in tuberculous animals. A tuberculous infection quantitatively increases it, but does not alter it qualitatively. It may be demonstrable as early as the third day after sensitization.

AUTHORS' SUMMARY.

CHEMICAL COMPOSITION OF THE ACTIVE PRINCIPLE OF TUBERCULIN: XV. FLORENCE B. SEIBERT and BETTY MUNDAY, Am. Rev. Tuberc. **25**:724, 1932.

Since the constituent of tuberculin which is responsible for producing cutaneous reactions in tuberculous animals is contained in the tuberculin protein molecule, methods are proposed and described for obtaining this protein in chemically pure form. These methods are: (1) growth on a pure nonprotein synthetic medium, (2) ultrafiltration, effecting concentration and purification, and (3) a single precipitation with trichloracetic acid. The chemical composition of the product TPT (tuberculin protein precipitated by trichloracetic acid), including nitrogen and polysaccharide content, varies only within 1 per cent, and the potency based on the nitrogen content varies almost within the range of experimental error of the skin test. Solutions of TPT are relatively stable, and stock solutions of any strength, equal to or greater than that of old tuberculin, can be made. A solution one and six-tenths times as strong as old tuberculin has been made. An equally potent and pure product can be made by means of ammonium sulphate precipitation, but the process is more tedious and does not readily lend itself to quantitative chemical work. Standardization of tuberculin potency should be made by means of the intracutaneous skin test, a known standard being used as control for diagnostic

purposes. Koch's old tuberculin was analyzed by the same methods, and 707 mg. of protein was obtained from 100 cc. This was approximately as active per unit of nitrogen as TPT. When old tuberculin was made in the usual way, but from a synthetic medium, the yield of protein precipitated by trichloracetic acid was 347 mg. per hundred cubic centimeters, exceeding the 295 mg. per liter obtained from a three month old culture of tuberculin on a synthetic medium and less than the 707 mg. per hundred cubic centimeters obtained from a sample of ordinary old tuberculin.

H. J. Corper.

Protection Against Tuberculosis With B C G in Guinea Pigs. Konrad E. Birkhaug, Am. Rev. Tuberc. **27**:6, 1933.

The tuberculinogenic principle of B C G is similar to that possessed by virulent bovine and human tubercle bacilli. No appreciable difference obtains in tuberculous guinea-pigs between the allergic cutaneous reactions elicited with tuberculins produced by virulent tubercle bacilli and B C G, whether whole or dissociated into "R" and "S" variant colony cultures. The oral administration of B C G in newly born guinea-pigs fails to arouse regularly tuberculin sensitization or any increased resistance to virulent superinfection. The parenteral administration of B C G in guinea-pigs is capable of arousing localized tuberculous lesions which heal promptly without producing progressive tuberculous disease. The parenteral B C G vaccination of guinea-pigs regularly produces tuberculin sensitization and a significant tuberculo-immunity which is most marked in animals vaccinated intracutaneously and subcutaneously. Guinea-pigs parenterally vaccinated with B C G are relatively twice as refractory to progressive tuberculosis following virulent superinfection as the nonvaccinated animals. Cultivation experiments demonstrate that B C G may survive in the body of the guinea-pig as long as five hundred and seventy-seven days after inoculation without showing any tendency to produce progressive tuberculosis. Parenteral administration in guinea-pigs of large doses of the S smooth colony variant dissociated from B C G is capable of arousing localized tuberculous lesions which heal promptly without producing progressive tuberculosis. B C G cultivated under partial anaerobiosis in deep broth cultures fails to show any increased virulence for guinea-pigs, but rather loses its viability after several months' cultivation. The experimental data presented indicate that B C G is harmless as a vaccine and is capable of arousing an outstanding and significant tuberculo-immunity when administered to guinea-pigs by parenteral routes.

Author's Summary.

A Rapid Method of Protecting the Peritoneum Against Peritonitis. B. Steinberg, Arch. Surg. **24**:308, 1932.

Protection against peritonitis can be obtained by the intraperitoneal injection of killed colon bacilli. Protection is due to the responding hyperleukocytosis and phagocytosis.

N. Enzer.

Skin-Reacting Substances in the Urine in Acute Streptococcal Infections. E. T. Conybeare, Bull. Johns Hopkins Hosp. **52**:119, 1933.

Colloidal material extracted from the urine of patients suffering from acute infectious conditions associated with beta hemolytic streptococci is capable, in a high proportion of cases, of producing a delayed erythematous reaction when injected intradermally into susceptible subjects. Similar material extracted from the urine of clinically normal persons is, by comparison on the same test subjects, relatively inactive as to the property of producing a cutaneous reaction. Such material from the urine of patients with scarlet fever appears to contain the "erythrogenic toxin" (Okell) of the hemolytic streptococcus. The reaction-

producing factor present in the material extracted from the urine of patients with acute pharyngitis and erysipelas is not shown by the experiments described to be derived from the hemolytic streptococcus. The possible nature of this factor is discussed.

AUTHOR'S SUMMARY.

IMMUNITY TO HUMAN AND PASSAGE POLIOMYELITIS VIRUS. SIMON FLEXNER, J. A. M. A. **99**:1244, 1932.

The passage of the virus of poliomyelitis through monkeys intensifies its infectivity for these animals and modifies its specific immunologic reactions. The changes undergone are quantitative and probably also qualitative. The modified virus preserves its immunizing power, in part at least, against recent strains of the human virus. Immune serums prepared with human and with monkey passage strains of virus exhibit quantitative differences in cross-neutralizing tests. Virus serum immunity can be produced in monkeys by the separate, simultaneous injection of one or more doses of virus and immune serum. The dangers of active poliomyelitic symptoms arising in the inoculated animals seem lessened by the combined treatment. The optimum manner of producing virus serum immunity has still to be determined. Monkeys that have proved wholly refractory to nasal instillations of the virus have been shown to be devoid of serum antivirus activity and to exhibit average susceptibility to the intracerebral inoculation of potent virus.

AUTHOR'S SUMMARY.

LOCAL SKIN REACTIVITY TO BACTERIAL FILTRATES. G. SHWARTZMAN, J. Exper. Med. **56**:677 and 687, 1932.

Reactivating Effect of Blood Serum on Neutralized Toxic Filtrates: In this paper there are reported observations on a certain new reactivating property of normal and immune blood serums of various animal species. The effect of the reactivating serums consists in restoration of the toxicity in vivo and in vitro of completely neutralized meningococcus and B. coli reacting factors. The property is apparently nonspecific and heat-labile, lessens on storage and has no relationship to complement. Heating of immune serums to a temperature destructive for the reactivating property, but innocuous to the neutralizing antibodies, raises considerably their neutralizing potency. The possible immunologic significance of the reactivating property is discussed in this paper.

Formation of Reacting Factors in Vivo: A rabbit sensitized a week previously to some animal protein receives a preparatory injection of a potent bacterial filtrate into the skin. Twenty-four hours later the rabbit is given an intravenous injection of the same animal protein. In from four to five hours severe hemorrhagic necrosis appears at the site of the preparatory injection. The incidence of positive results is high. A single sensitizing injection and an incubation period of one week are sufficient. The test is highly specific unless repeated sensitizing injections of large doses of antigen are made. The necessary sensitization can be elicited with minute quantities of animal proteins. It is also possible to elicit severe reactions at the sites of the preparatory injections in nonsensitized rabbits on separate intravenous injections of nonbacterial antigens and homologous antibodies (i. e., passive transfer.)

AUTHOR'S SUMMARIES.

PREVENTION OF BARTONELLA ANEMIA IN RATS. D. PERLA and J. MARMORSTON-GOTTESMAN, J. Exper. Med. **56**:777 and 783, 1932.

An aqueous lipoid extract of ox spleen was prepared which protects adult male albino rats of carrier stock in a large percentage of instances against Bartonella muris anemia following splenectomy. It is suggested that the extract contains a specific hormonal substance.

Copper plays a rôle in the mechanism of resistance to Bartonella muris anemia in the rat. The small amount of the element in the ordinary diet of the rat is insufficient to protect the animal after splenectomy. An excess of copper, however, may give protection in the absence of the spleen. Its utilization would seem to be intimately associated with splenic function.

AUTHORS' SUMMARIES.

THE MATERNAL TRANSMISSION OF VACCINAL IMMUNITY IN SWINE. J. B. NELSON, J. Exper. Med. **56**:835, 1932.

The introduction of vaccinia virus into the skin of swine calls forth a typical vesicular reaction which may be followed by a solid immunity. This acquired state of resistance was utilized in determining the route of immunity transmission from sow to young. The suckling young of immune sows, vaccinated on the seventh day or earlier, showed no reaction to the virus. Their hand-fed litter mates, however, were susceptible and reacted with the formation of vesicles. These observations indicate that the porcine placenta is largely impermeable to protective substances, and establish the fact that colostrum functions as the vehicle for their transmission as it does for antibodies.

AUTHOR'S SUMMARY.

ADVANTAGE OF VIRULENT SMOOTH STRAINS OF TYPHOID BACILLI FOR VACCINES. F. B. GRINNELL, J. Exper. Med. **56**:907, 1932.

A study of the subcultures of the Rawlins strain of Bacterium typhosum used by twelve different laboratories for the production of vaccine showed that they all differed from recently isolated smooth strains in cultural characteristics, virulence and protective efficiency. Eleven of these Rawlins cultures gave both the flagellar and the somatic type of agglutination in antismooth rabbit serum, and the one culture so tested produced both flageliar and somatic agglutinins when injected into rabbits and man. Agglutination of neither the flagellar nor the somatic type can therefore be used as a test of the smoothness of a culture or as an index of immunity. Since the Rawlins strain differs from the smooth phase of Bacterium typhosum in cultural characteristics and in virulence and is much less efficient than smooth strains as a protective antigen, and since the selection and maintenance of smooth cultures suitable for vaccine production present no serious difficulty, it would seem but logical to substitute virulent, smooth cultures for the very old Rawlins strain, if one is to expect the maximum protection from antityphoid vaccination.

AUTHOR'S SUMMARY.

ACTIVE IMMUNIZATION OF MICE WITH THE POLYSACCHARIDES OF PNEUMOCOCCI, TYPES I, II AND III. J. ZOZAYA and J. CLARK, J. Exper. Med. **57**:21, 1933.

Pneumococcus polysaccharides, types I, II and III, adsorbed on collodion particles, and types I and III, adsorbed on carbon (nori), are antigenic in mice. Unadsorbed pneumococcus polysaccharide of type I is antigenic in mice in proper dilution. One preparation of type II polysaccharide is not antigenic, while another one immunized against types I and II. Type III polysaccharide is only slightly antigenic against type III, but immunized against type I. The antigenicity of pneumococcus polysaccharide in optimal dosage is tentatively explained by an adsorption phenomenon taking place in the body in instances in which the polysaccharide has not been adsorbed before injection. The aggressin-like action of large doses of pneumococcus polysaccharides, types I, II and III, is further established.

AUTHORS' SUMMARY.

IMMUNOLOGICAL REACTIONS BETWEEN AGAR-AGAR AND SOME BACTERIAL ANTISERA. J. ZOZAYA and L. MEDINA, J. Exper. Med. **57**:41, 1933.

As found by Sordelli and Mayer, agar adsorbed on bacteria produces agar-reacting antibodies in animals receiving injections of these organisms. False cross-

agglutination and precipitin reactions can be produced in serums containing agar-reacting antibodies by organisms grown on agar. Zozaya's publication in this field requires partial revision on this account. There is suggestive immunologic evidence of chemical similarity between the specifically reactive groups of agar-agar, and the C substance of the pneumococcus. AUTHORS' SUMMARY.

HUMAN IMMUNITY REACTIONS TO PNEUMOCOCCI OTHER THAN TYPES I, II AND III. M. FINLAND and W. D. SUTLIFF, J. Exper. Med. **57**:95, 1933.

A group of seventy-two human subjects were studied with respect to the immune reactions of their blood and serums to pneumococci, types I, II and III, and to four other types (V, VI, VIII and IX) previously included in group IV. The same general relationships were observed for all of these types as were previously demonstrated for types I, II and III. Each type was specific in relation to the bactericidal action of normal human blood and the protective action of normal human serum. The frequency with which pneumococcidal action for any pair of types was present for both or absent for both in the same samples of blood was slightly greater than that calculated from the frequencies with which each of the types was killed separately. No closer correlation could be demonstrated between the reaction of the blood of these subjects to types II and V and the reaction to types III and VIII (types related in their reaction to artificially prepared immune serums) than was observed between unrelated strains. AUTHORS' SUMMARY.

ALLERGIC LOBAR PNEUMONIA. B. M. FRIED, J. Exper. Med. **57**:111, 1933.

The injection of small amounts (1 cc.) of horse serum into the lungs of normal rabbits produces a transient pneumonitis confined to the dorsal aspect of both lungs. The injection of the same amount of horse serum into the lungs of rabbits that have been previously sensitized to the same serum causes, in a high percentage of cases, a lesion which is confined to one lung, with the gross and microscopic features of lobar (fibrinous) pneumonia in man. AUTHOR'S SUMMARY.

NATURAL AND ACQUIRED RESISTANCE IN PROTOZOA TO THE ACTION OF ANTIGENIC POISONS. C. H. PHILPOTT, J. Exper. Zoöl. **63**:553, 1932.

Venoms have been found to be very satisfactory as representative antigenic poisons for use in the study of natural and acquired resistance in protozoa to agents that produce immunity in higher animals. Paramecia belonging to the same clone, but grown in different environments, show less difference in resistance to venoms than animals of different clones grown in similar environments. Thus it seems that genetic factors are more important under ordinary conditions than environmental factors in determining resistance in Paramecia. The resistance to venom in a clone of Paramecia gradually decreases when the animals are grown for long periods of time in uniform culture mediums. The resistance to venom in a clone of Paramecia fluctuates from time to time, even when the animals are grown under uniform conditions. This fluctuation in resistance is general rather than specific; i. e., at the time that the resistance increases or decreases for one venom, it changes correspondingly for another. When Paramecia are exposed at intervals through long periods of time to the action of a venom, hypersensitiveness to the poison first develops. As treatments are continued the animals gradually recover from this and display a certain amount of resistance. This resistance is never great, and in this respect resembles the tolerance which animals acquire to ordinary poisons rather than immunity to antigens. The acquired resistance is specific in the sense that resistance to a venom does not protect the animals from an unrelated venom. The acquired resistance is also temporary and is soon lost when the animals are no longer treated. AUTHOR'S SUMMARY.

STUDIES IN ANAPHYLAXIS IN THE RABBIT. ELLA F. GROVE, J. Immunol. **23**:2, 101, 1932.

The technic employed by Grove brought about maximal sensitiveness to egg white and horse serum in 70 per cent of rabbits, while about 25 per cent remained insensitive. Different modifications of the technic gave inferior results. A subcutaneous injection one week after the peak of sensitiveness was reached led to a diminution of sensitiveness, but did not influence the titer of the antibodies. There was no direct connection between the degree of precipitin production and sensitization though in the rabbits treated with egg white the passively sensitizing property of their serum was, in general, parallel to the precipitin titer. The development of the Arthus phenomenon was no criterion of the degree of sensitization. It was present without a high degree of sensitization, and vice versa. The lack of response to sensitization in about 25 per cent of rabbits was not due to hyposensitivity of their shock tissues, as evidenced by the observation that they died with anaphylactoid symptoms following injections of barium chloride, which, in smaller doses, acts primarily on the shock tissues affected in the general anaphylactic reaction. There were differences in the response of unstriped muscles from various parts of the body of rabbits and guinea-pigs to the addition of histamine, epinephrine and barium chloride to the Dale bath. The same substances produced different responses in the different muscles, and the same muscles reacted differently to the different substances. The effect of these substances in the living animal was not always reflected in the action on the isolated muscle. Rabbits became uniformly and maximally sensitized with fowl corpuscles. Aqueous extracts of fowl corpuscles had only slight antigenic qualities in vitro and none in vivo. Rabbits treated with goose corpuscles yielded immune serums toxic for guinea-pigs. The ability of guinea-pig kidney to absorb the toxic substance throws some doubt on the view that goose corpuscles are free from Forssman's antigen. The Arthus phenomenon was observed in almost all rabbits sensitized with fowl corpuscles. Spiral strips of the pulmonary artery of sensitized rabbits contracted in the Dale bath after addition of the specific antigen, while the bronchial strip did not show this response. The response of the bronchial strip to histamine was slight. The weakness of the unstriped musculature of the bronchus explains that phenomenon. The experiment corroborates the view of Simonds concerning the symptomatology of acute anaphylactic shock in rabbits. The absence of contraction of the urinary bladder in rabbits was to Manwaring an evidence of lack of participation of unstriped muscle in acute anaphylactic shock in that animal. Grove showed that in the guinea-pig contractions of the urinary bladder are due to asphyxia. This condition is absent in the rabbit, and therefore contraction of the bladder does not occur. When asphyxia is produced experimentally, contractions of the bladder also result.

I. DAVIDSOHN.

AGGLUTINATION REACTIONS IN RHEUMATOID ARTHRITIS. MARTIN H. DAWSON, MIRIAM OLMSTEAD and RALPH H. BOOTS, J. Immunol. **23**:187, 1932.

Serums of patients with rheumatoid arthritis agglutinated in high dilutions strains of hemolytic streptococci, coming from different sources, equally as well as the so-called typical strains of Cecil, Nicholls and Stainsby. Of various other gram-positive cocci, only R strains of pneumococci were agglutinated in high dilutions. Serums of patients suffering from different diseases possessed only very low agglutinating properties for the hemolytic streptococci. Serums of normal controls did not agglutinate at all. The agglutinating titer rises with the duration of the disease and with the age of the patient. Absorption experiments showed lack of specificity among the various agglutinated strains of hemolytic streptococci. The R pneumococci absorbed the agglutinins from the patients' serums but not as fully as the streptococci. The agglutinins show the same thermal properties as normal antibodies. In no case could streptococci be isolated from the blood of patients suffering from rheumatoid arthritis. Dawson and his associates

emphasize that there is no compelling evidence of a relationship between the presence of agglutinins in the blood and the etiologic rôle of hemolytic streptococci in the production of the disease.

I. DAVIDSOHN.

TUBERCULIN TESTS IN INFANTS VACCINATED WITH B C G. R. DEBRÉ, M. LELONG and PICTET, Ann. Inst. Pasteur **49**:4, 1932.

Careful tuberculin tests were performed periodically on 297 infants vaccinated by mouth with B C G and on 193 unvaccinated infants. Both groups were under adequate control, and were protected from contact with tuberculosis. The large control group, members of which consistently presented negative reactions, is offered as a measure of the rigorous control in the technic used. In the vaccinated group 97 per cent showed positive reactions at 2 years, the maximum. At 3 months, 73 per cent showed reactions; at 6 months, 89 per cent, and at 1 year, 91 per cent. The degree of sensitivity increased with age also, during this period, and thereafter remained constant at least up to 5 years, the age limit of the group tested.

AUTHORS' CONCLUSIONS.

CUTANEOUS PASSIVE IMMUNIZATION AGAINST TETANUS. A. URBAIN, Ann. Inst. Pasteur **49**:103, 1932.

Favorable results were secured in the prevention and cure of tetanus intoxication or infection in guinea-pigs. Tetanus antitoxin, of a potency of 3,000 units (international) per ten cubic centimeters, was mixed with a petrolatum and hydrous wool fat base. The ointment, in lethal doses, was applied to the shaven and slightly scarified skin of test animals between twenty-four hours preceding the injection either of toxin or of spores mixed with staphylococci and three hours after such injections. This afforded a fair degree of protection; the action was specific.

M. S. MARSHALL.

SANARELLI AND SHWARTZMAN REACTIONS. A. GRATIA and R. LINZ, Ann. Inst. Pasteur **49**:131, 1932.

The Sanarelli reaction (1924) was based on the observation of rapid death in an animal given an intravenous injection of a tolerated dose of cholera organisms and, the next day, a filtrate of an otherwise harmless organism, like Proteus, by the same route. The Shwartzman reaction (1928) is based on the local skin reaction at the site of injection of an innocuous filtrate when a similar filtrate is given intravenously the next day. In an exhaustive study the authors conclude that the phenomena are identical, and they reveal many positive and negative factors too numerous to abstract properly. Young rabbits and guinea-pigs gave reactions; rats and mice did not. Observation of the skin of rabbit ears had certain advantages, but the intestines, kidneys and lungs also showed hemorrhagic reactions. At least five or six hours were necessary between injections. In a strong reaction circulatory changes similar to those observed in anaphylaxis occurred. Intravenous injections of a filtrate of Bacterium coli produced hemorrhagic reactions in animals prepared with a number of visible and invisible viruses. It is believed that a number of clinically observed hemorrhagic conditions are based on similar phenomena.

M. S. MARSHALL.

VASCULAR REACTIONS IN ISOLATED ORGANS. V. ZERNOFF, Ann. Inst. Pasteur **49**:358, 1932.

"The method of isolated vessels permits the study of vascular reactions in a simple and precise manner. Bacterial cultures (Danysz' bacillus, heated Vibrio cholerae) have no pronounced action. . . . Tuberculin provokes vascular contraction. Toxins of diphtheria, tetanus and Clostridium edematiens produced a

strong contraction. The method permits the study of anaphylactic shock in vitro. The passage of antigen induces a violent contraction of isolated peripheral vessels of sensitized animals. . . . Horse serum produces no reaction in the isolated vessels of nonsensitized animals. The sensitivity of isolated vessels may be controlled by epinephrine. They react to dilutions of 1:10,000,000. After isolation of a rabbit's ear the life of the vessels may be preserved for several days (eighteen days and longer). The death of the organism does not signify the death of the tissues."

M. S. MARSHALL.

VACCINATION AGAINST TYPHUS. CHARLES NICOLLE and HÉLÈNE SPARROW, Arch. Inst. Pasteur de Tunis **21**:25, 1932.

The method of Weigl, consisting of vaccination by means of a phenolized suspension of the intestines of infected lice, was tested. Although Old World typhus is less dangerous to laboratory workers than American strains, the Weigl vaccine is being used, since all experimental tests were favorable.

M. S. MARSHALL.

SKIN REACTIONS TO VARIOLA, VACCINIA AND VARICELLA. PAUL DURAND and ERNEST CONSEIL, Arch. Inst. Pasteur de Tunis **21**:73, 1932.

Variola or vaccinia left a state of skin reactivity to either virus. This was not true of varicella; there was no reaction with varicella virus or with the heterologous viruses. The reaction is considered an immunity reaction, distinct from the sensitivity group (tuberculin and others) and the "reactivity" group (diphtheria toxin, etc.). Varicella is thus considered as distinctly separate from related vaccinia and variola, and a means of checking relationships between animal pox diseases is afforded. The technic used consisted of intradermal inoculations of specially prepared antigen, following which local reactions were relatively rapid (in four or more hours). The phenomenon is thus not the usual immunity reaction to vaccine virus, the disadvantages of which are pointed out by the authors.

M. S. MARSHALL.

ANAPHYLACTIC SHOCK IN TISSUE CULTURES. ENRICO SERENI and LIVIA GAROFOLINI, Arch. f. exper. Zellforsch. **13**:53, 1932.

If cells of the spleen, bone marrow or epiploon of a chicken sensitized against horse serum are cultured in a medium to which small amounts of the antigen are added (from 1:10,000 to 1:20,000), an anaphylactic shock occurs, manifesting itself by extensive cellular degeneration. The hypersensitivity is, however, preserved only up to the third passage in a normal medium. Cells can also be sensitized in vitro by adding small amounts of the antigen to the medium. The sensitization develops quickly and disappears after six or seven days (three passages). An active sensitization against the antigen in vitro cannot be obtained if cells of other organs (heart, kidney, liver, stomach, testis) are used. It occurs, however, if these tissues are explanted in a sensitized serum. A passive sensitization of these tissues is therefore possible. An active sensitization is obtained when liver and spleen present in the culture medium, as the splenic tissue apparently excretes antibodies into the medium. The anaphylactic antibody formation is exclusively bound to the hematopoietic organs.

WILHELM C. HUEPER.

THE TEMPORAL FACTOR IN THE APPEARANCE OF IMMUNITY IN EXPERIMENTAL TUBERCULOSIS. E. BRUDNICKI, Beitr. z. Klin. d. Tuberk. **81**:579, 1932.

Endeavoring to determine the time relationship between primary tuberculous infection and the appearance of detectable immunity, guinea-pigs were reinfected at

progressively greater intervals. It was found that the shortest interval between infection and reinfection in which altered reaction to the latter could be demonstrated was four days. The differentiation became more striking as the time interval was increased.

AARON EDWIN MARGULIS.

SUSCEPTIBILITY TO SCARLET FEVER AND BLOOD GROUPS. H. NAVAK, Monatschr. f. Kinderh. **54**:343, 1932.

Evidence is presented in favor of a greater susceptibility to scarlet fever in children of group O than in children of group A.

MORPHOLOGIC BLOOD PICTURE IN HUNGER AND IN ENTERAL SENSITIZATION AND ANAPHYLAXIS. W. N. NEKLUDOW and E. A. NEKLUDOWA, Virchows Arch. f. path. Anat. **280**:374, 1931.

Several series of guinea-pigs were sensitized to egg albumin by the enteric route. Reintroduction of the same antigen into the stomach from two to three weeks later resulted in anaphylactic shock. Hunger intensified these reactions by making the mucous membrane of the gastro-intestinal tract more permeable to the foreign protein. Eosinophilia was noted during the period of sensitization and during shock, but was even higher after oft-repeated enteric introduction of the foreign protein. During shock there is an increase of the pseudo-eosinophils and a fall in lymphocytes.

PERRY J. MELNICK.

ALLERGIC TISSUE REACTION DUE TO HOMOLOGOUS BLOOD. H. GEISSENDÖRFER, Virchows Arch. f. path. Anat. **285**:385, 1932.

To determine whether the local allergic tissue reaction that follows the introduction of a foreign antigen is due to the fact that the antigen is foreign to the species, the author injected whole guinea-pig blood into guinea-pigs. In one series each animal received its own blood, and in another series blood from other animals of the same species. The injections were made subcutaneously or intraperitoneally. The first injection consisted of 1 cc. of blood; the second, of 0.5 cc. introduced twenty-one days after the first. The first injection of the animal's own blood caused no local reaction. The first injection of the blood of another animal of the same species caused a slight lymphocytic and monocytic reaction. The second injection induced a local reaction identical qualitatively with that following the injection of heterologous blood, but somewhat less marked in degree.

O. T. SCHULTZ.

Tumors

ANALYSIS OF ONE HUNDRED AND FOUR CASES OF CARCINOMA OF THE LARGE INTESTINE. H. T. KARSNER and B. CLARK, JR., Am. J. Cancer **16**:933, 1932.

Carcinoma of the large intestine may assume projecting or polypoid, infiltrating and ulcerative and stenosing forms. Excess production of mucus may occur in any of the forms, but most often observed in the infiltrating, well differentiated adenocarcinomas. The term mucinous carcinoma is literally more correct than colloid carcinoma. The character of the tumor is determined by its cellular content and arrangement rather than by its incidental production of mucin. Extension and metastasis of rectal cancers are somewhat more frequent than of cancers of the colon, probably owing to differences in lymphatic drainage. Widespread metastasis is infrequent. Lymph nodes may be notably hyperplastic and not the seat of metastasis. Adenomatous polyps frequently become malignant. It is not established that all cancers of the large intestine originate in adenomatous polyps, but it may well be that this is true of about 40 per cent. The presence of marginal

adenomatous polyps may be an irritation phenomenon and not a proof of the origin of the cancer from polyps. Grading on the basis of microscopic criteria makes it probable, as regards rectal cancers, that as anaplasia increases, the age incidence, duration of symptoms and length of life decrease. In the series of cancers of the colon reported here, the higher degrees of anaplasia in cancers of the cecum and ascending colon affect the figures for the entire colon, so that the grades are definitely of higher order in the colon than in the rectum. This has yet to be established satisfactorily on the basis of a sufficient number of observations. It may serve as a basis of comparison of malignancy in tumors of the colon, but does not indicate practically that they are more malignant than rectal cancers.

FROM AUTHORS' SUMMARY.

PRIMARY TUMORS OF THE OS CALCIS. B. L. COLEY and G. S. SHARP, Am. J. Cancer **16**:1053, 1932.

The os calcis is an infrequent site of a primary bone tumor; but thirty-two cases were found in a combined study of the records of the Bone Tumor Department of Memorial Hospital and of the Bone Sarcoma Registry of the American College of Surgeons. Indefiniteness of clinical manifestations and of roentgenographic findings makes a positive preoperative diagnosis extremely difficult. An accurate diagnosis is essential for correct treatment. It follows that this can be obtained in most cases only by histologic study. If aspiration biopsy is inconclusive, as it often is, a surgical biopsy is indicated. In osteogenic sarcoma the treatment is early amputation. We do not favor prolonged irradiation preliminary to amputation, but, if adequate radiation can be delivered in a brief period, followed promptly by amputation, we see little objection to its employment; we have no data to suggest that the results are thereby improved. Endothelial myeloma, being an extremely radiosensitive tumor and characterized by early and wide dissemination to other bones as well as the lungs, is best handled by irradiation with high voltage x-rays and injections of mixed toxins of erysipelas and Bacillus prodigiosus. A giant cell tumor may be treated successfully by irradiation alone. There are, however, a number of cases of tumors in other bones in which irradiation has been used in the past in doses that have caused permanent damage to the skin, soft parts and bone. The response to irradiation varies considerably in individual cases of giant cell tumors. Thorough curettage, followed by an escharotic, such as zinc chloride or phenol and alcohol, is an established method of dealing successfully with these cases, particularly when the tumors are well defined and have not broken through the cortex and extended into the soft parts. The combined case records of the Memorial Hospital and the Bone Registry show that an early, correct diagnosis was seldom achieved, and that there was no well conceived plan of treatment for primary tumors of the os calcis.

AUTHORS' SUMMARY.

XANTHOMA OF THE BREAST. C. D. HAAGENSEN, Am. J. Cancer **16**:1077, 1932.

Xanthomas in general have been discussed, and tumors of the breast containing xanthoma cells have been classified as follows: primary xanthoma, a very rare tumor composed wholly of xanthoma cells and arising as a local manifestation of the syndrome of xanthomatosis; secondary xanthomatous degeneration, frequently encountered in true neoplasms, inflammatory processes and traumatic fat necrosis. Three cases of primary xanthoma of the breast and illustrative cases of secondary xanthomatous degeneration occurring in fibro-adenoma, in chronic abscess of the breast and in traumatic fat necrosis in the breast have been described.

AUTHOR'S SUMMARY.

LIPOMA. F. E. ADAIR, G. T. PACK and J. H. FARRIOR, Am. J. Cancer **16**:1104, 1932.

The salient clinical features of 352 lipomas occurring in 134 patients are reported. A clinicopathologic classification of lipomas is given, with illustrative case reports. Evidence is submitted in support of the theory that multiple lipomas are neurogenic tumors.

AUTHORS' SUMMARY.

GENETIC STUDIES ON THE TRANSPLANTATION OF TUMORS. J. J. BITTNER, Am. J. Cancer **16**:1144, 1932.

Rhythms of growth do not occur in the transplanted tumor cell. The theories of adaptation and virulence are no longer necessary. Intrinsic genetic factors determine the physiologic characteristics of both the host and the tumor cell.

AUTHOR'S SUMMARY.

THE MALIGNANT CELLS OF WALKER RAT SARCOMA No. 338. M. R. LEWIS and W. H. LEWIS, Am. J. Cancer **16**:1153, 1932.

The malignant cells of the Walker rat sarcoma 338 differ from normal fibroblasts. They are larger, the cytoplasm is denser and more granular, and the mitochondria are smaller and more numerous. Their nucleus is large and granular and shows no nucleoli. There is a pronounced central area. There are more cells with two or more nuclei than are found in cultures of normal fibroblasts. The number of atypical, abortive and abnormal mitoses is far greater than in cultures of normal cells, and there is apparently great variation in the number of chromosomes. Aberrant chromosomes are common. They form chromosome vesicles. The duration of mitosis, especially the metaphase, is prolonged. It has been suggested that malignancy may be bound up with permanent alteration of the centrosomal apparatus rather than with abnormal chromosome complexes, and that the latter are the result of the former.

AUTHORS' SUMMARY.

SOLITARY MYELOMA (PLASMACYTOMA) OF THE FEMUR. W. G. HARDING, JR. and T. S. KIMBALL, Am. J. Cancer **16**:1184, 1932.

A case of solitary plasma cell myeloma of the femur is reported. The nine cases of solitary myeloma recorded in the literature are reviewed. Complete roentgenographic and postmortem examinations were made in the case reported.

AUTHORS' SUMMARY.

IS THE INCREASE OF CANCER REAL OR APPARENT? M. T. MACKLIN, Am. J. Cancer **16**:1193, 1932.

Cancer is increasing, and it is increasing particularly in the age group over 60. It is not occurring at progressively younger ages or attacking larger percentages of the younger population. Despite the increase in cancer, deaths are fewer from all causes now than they were. More ground has been won from the ravages of infectious disease than has been lost to those disorders which are dependent on qualities inherent in the chemical and physical make-up of the patients. Cancer is increasing because, by preventive methods, there has been created a larger population to grow old, and, having grown old, they are kept from dying of those ills from which they formerly suffered. With each increase in the warfare against preventable diseases, there will be an increase in the ravages of cancer, for with each victory there is created a greater population to die from that disease. These conclusions are based on the statistics of Canada. There is strong ground for believing that a similar analysis of the statistics of any other country would lead to the same conclusions. It is true that there may be racial differences in immunity

to cancer, but the conclusion here reached will probably prove universal, namely, that excellent measures for the public health and high cancer rates are inseparable, at least for the present. Those who point to the low cancer rates existing among primitive peoples and who state that cancer is a disease of modern civilization neglect to call attention to the fact that preventive medicine is itself a triumph of modern civilization.

AUTHOR'S SUMMARY.

"FIBROMYOSIS": AN UNCLASSIFIED PLEXIFORM ENDOLYMPHATIC PROLIFERATION OF THE UTERUS. R. T. FRANK, Am. J. Cancer **16**:1326, 1932.

Based on the study of three cases of strikingly similar nature, the following conclusions seem warranted. Diffuse endolymphatic fibromyosis of the uterus, although rare, appears to form a distinct entity. The onset is characterized by marked and repeated uterine hemorrhages. A slow, uniform and symmetrical enlargement of the uterus occurs. From the findings a clinical diagnosis of myoma or adenomyoma is warranted. At operation the findings are such as to justify a similar diagnosis, and consequently supravaginal hysterectomy is performed. From the gross specimen, the pathologist makes the diagnosis of diffuse adenomyosis or functional "fibrosis." Microscopic study shows diffuse endolymphatic distribution with no evidence of a primary site. The endometrium is normal. From the cases so far observed, this type of neoplasm appears to be slow-growing and with only a moderate degree of clinical malignancy. No final conclusion as to its radiosensitivity can as yet be offered.

AUTHOR'S SUMMARY.

XERODERMA PIGMENTOSUM. M. M. COPELAND and H. E. MARTIN, Am. J. Cancer **16**:1337, 1932.

Four cases of xeroderma pigmentosum are reported. The disease begins early in life, usually before the second year. The manifestations of the disease are reddening and pigmentation (lentigines) followed by roughening, dryness and ulceration of the skin. These changes are often associated with the formation of telangiectases and tumor-like processes, including basal cell and squamous cell carcinoma. The clinical course is characterized by progressive changes with moderate remissions, invariably running a prolonged but fatal course. The principal exciting cause seems to be exposure to the actinic rays of the sun in patients predisposed to the disease. The occurrence of the predisposition has been ascribed to a congenital susceptibility. While the skin has been considered the site of the predisposition, it is not clear what rôle is played by chemical disturbances in the blood and peripheral tissues. A trophoneuritic or nervous origin has been suggested, but there is lack of proof, and this is no longer considered feasible. Hematoporphyrin (a photodynamic substance) has been recently cited as a possible factor in bringing about the disease. The data at hand do not support the contention that a photodynamic substance is a causative factor in xeroderma pigmentosum. Disturbances in the glands of internal secretion are not as yet correlated with the disease process. Treatment has been divided into two major groups: treatment directed toward checking the progress of the disease and that directed toward curing certain local manifestations, such as ulcerations and neoplastic processes.

AUTHORS' SUMMARY.

BENIGN TUMORS OF THE BRONCHUS. P. GEIPEL, Frankfurt. Ztschr. f. Path. **42**: 516, 1932.

The author describes a case of basal cell carcinoma of the bronchus and a case of adenomatous polyp of the bronchus. The literature of benign bronchial tumors is reviewed.

O. SAPHIR.

MULTIPLE MYELOMA WITH DIABETES INSIPIDUS. H. G. ARONSOHN, Virchows Arch. f. path. Anat. **281**:78, 1931.

Aronsohn reports a case of multiple myeloma in which diabetes insipidus developed in the final few weeks before death; he states that this symptom in multiple myeloma has been reported only twice previously. At necropsy, it was found that a tumor mass growing in the sphenoid had produced localized defects in the floor of the sella turcica and in the body of the sphenoid. Aronsohn ascribes the diabetes insipidus to the action of the tumor on the hypophysis, but leaves undecided whether it acted directly on the gland or only interfered with the blood supply of the gland.

O. T. SCHULTZ.

CARCINOMA OF THE PROSTATIC URETHRA WITH IMPLANTATION METASTASIS IN THE ANTERIOR URETHRA. W. GEISLER, Virchows Arch. f. path. Anat. **281**: 88, 1931.

A man, aged 64, who died of urosepsis following urinary retention, was found at necropsy to have a primary papillary carcinoma of the prostatic urethra. The tumor was very cellular and anaplastic. The fossa navicularis was occupied by an implantation metastasis of similar character that was not visible at the external urethral orifice. In the literature, primary carcinoma of the urethra is more frequent in women than in men.

O. T. SCHULTZ.

LOCAL ALLERGY AND HYPERKERATOSIS. O. REUTERWALL, Virchows Arch. f. path. Anat. **281**:483, 1931.

This experimental investigation had its inception in the thought that cancer may be a local allergic manifestation. Egg white was injected subcutaneously into the ears of rabbits. The injections were usually repeated twice a week over long periods of time and were always made into the same area. Reinjection led to an acute local anaphylactic reaction. In some of the animals this reaction was followed by hyperkeratosis of the ear. Only one such lesion regressed spontaneously. Animals with persisting hyperkeratotic lesions had not been under observation long enough to determine whether the epithelial proliferation would assume the characteristics of malignancy.

O. T. SCHULTZ.

CARCINOMATOUS MURAL THROMBOSIS OF THE HEART. R. WINTER, Virchows Arch. f. path. Anat. **282**:99, 1931.

In a case of carcinoma of the pancreas, the tumor spread by way of the portal vein and the inferior vena cava. Multiple thrombi were present on the endocardium of the right side of the heart, on the tricuspid valve and on the chordae tendineae of the tricuspid. The more recent thrombi contained tumor cells. Carcinoma cells were not present or were in a state of degeneration in organized thrombi. Winter believes that emboli of tumor cells became attached to the endocardium, which they destroyed by their proteolytic activity. A thrombus formed at the point of denudation, the carcinoma cells being enmeshed in the thrombus. As the thrombus organized, the tumor cells degenerated and eventually disappeared. A similar process was observed in the larger branches of the pulmonary artery. Tumor emboli that completely occluded terminal arterioles and capillaries did not lead to thrombosis and were able to grow through the walls of the vessels and to establish themselves as metastases.

O. T. SCHULTZ.

Medicolegal Pathology

PENETRATION OF FLUIDS INTO THE RESPIRATORY AND DIGESTIVE SYSTEMS FOLLOWING SUBMERSION OF DEAD BODIES. B. MUELLER, Deutsche Ztschr. f. d. ges. gerichtl. Med. **19**:488, 1932.

Experiments on eighteen corpses of adults showed that a few minutes after submersion fluids had entered the trachea down to the middle-sized bronchi, the

esophagus and, in a few cases, the stomach; fluids were never found in the duodenum or in the peripheral areas of the lungs. Submersion of twenty-two dead bodies of new-born infants disclosed that fluids would penetrate the upper respiratory tubes, the esophagus and the stomach if the infants had been born alive and had breathed. The same findings were encountered in stillborn babies if artificial respiration had been applied prior to submersion, because of air being forced in to inflate the lungs and stomach. Escape of gas present in the stomach or in the air passages while the dead body was submerged allowed the fluids to penetrate the lungs and stomach rapidly.

E. L. MILOSLAVICH.

METHODS OF PERFORMING ILLEGAL ABORTIONS. M. MAGID and M. WENZKOWSKY, Deutsche Ztschr. f. d. ges. gerichtl. Med. **19**:501, 1932.

A statistical study is made of 891 women with a history of 4,264 abortions, 133 of which were self-induced and 114 of which were performed by lay people. As to the technic applied, the cases are divided into five main groups: (1) external methods (hot baths, abdominal massages and the deliberate lifting of heavy objects); (2) peroral methods (ingestion of various drugs and poisons); (3) vaginal methods, such as douches; (4) intra-uterine methods (irrigations and foreign bodies), and (5) curettement. Various intra-uterine procedures were the most frequent, even in self-induced abortions (43 per cent), and were constantly employed by midwives, doctors and lay people. Introduction of a catheter or bougie was practiced in 42.4 per cent of the cases, and irrigations with, or injections of, soap solutions in 11.7 per cent. Quinine was taken perorally in 5.3 per cent.

E. L. MILOSLAVICH.

INFANTICIDE BY NEEDLE PUNCTURES. A. UCKE, Deutsche Ztschr. f. d. ges. gerichtl. Med. **19**:508, 1932.

A 20 year old girl thrust sewing needles and safety pins into her 10 day old illegitimate baby, causing its death from septicemia with purulent pericarditis and bilateral pleurisy ten days afterward. A fragment of a sewing needle was found protruding into the right ventricle of the heart, and the eye-end of another needle was projecting above the external surface of the left lobe of the liver. The broken-off point of a safety pin was found free in the exudate of the left pleural cavity, while another broken-off safety pin lodged within the lower lobe of the right lung. The microchemical examinations of the injured tissues proved the presence of iron particles.

E. L. MILOSLAVICH.

SUICIDE BY SELF-MUTILATION AND DROWNING. JACOBI, Deutsche Ztschr. f. d. ges. gerichtl. Med. **20**:64, 1932.

A farmer's wife completely severed her left hand at the wrist line with a hatchet and then drowned herself in manure-water. Inside the barn, a blood-stained wooden chopping-block, on which she had rested her left arm, the bloody hatchet, and the cut-off left hand were found. On the volar ulnar aspect of her left forearm, five additional deep cuts were evident. Self-mutilations of this kind may mislead one into assuming that the person has been murdered.

E. L. MILOSLAVICH.

EXTENSIVE ENCEPHALOMALACIA FOLLOWING TRAUMATIC LACERATION OF THE COMMON CAROTID. E. SCHWARTZ, Deutsche Ztschr. f. d. ges. gerichtl. Med. **20**:67, 1932.

A 39 year old woman sustained, in an automobile accident, a deep tear on the left side of the neck, and the left common carotid was completely severed.

One hour after ligation of the artery and vein, a left-sided hemiplegia developed, and death ensued after two days. Within the left cerebral hemisphere an extremely large area of softening extending up to the brain cortex was found. Thrombotic and embolic processes were absent, and the blood vessels did not exhibit atherosclerotic changes.

E. L. MILOSLAVICH.

HISTOLOGY OF ELECTRIC CURRENT AND LIGHTNING MARKS. M. NIPPE, Virchows Arch. f. path. Anat. **285**:1, 1932.

In the mark made by the electric current in the skin when uncomplicated by actual burning, the epidermis contains cleftlike spaces and groups of small rounded spaces separated by a fine meshwork; the epithelium is clumped, and groups of the cells of the malpighian layer have a palisade arrangement and an altered direction. These changes, which are characteristic, Nippe ascribes to the action of heat, which drives water out of the cells. The altered direction of the cells of the malpighian layer is not due to the course of the current, as claimed by some, but to wavelike physical alterations brought about by the current, such as may occur in a wire when a strong current is sent through it. The mark made by lightning differs grossly from that made by the electric current. The former consists either of a group of numerous, closely placed, minute, hemorrhagic points, from which the surface epithelium has disappeared, or of fine, branching, dendritic streaks. Histologically, the difference between the two kinds of marks is even more striking. In the case of lightning stroke, described in considerable detail by Nippe, there was no burning of the skin or singeing of the clothing, although the felt hat worn had been torn to shreds. There were numerous lightning marks on the right side of the body. In the marks the superficial portion of the epidermis had been separated from the deeper portion, but neither part of the epidermis revealed the changes characteristic of the current mark. The capillaries of the corium were engorged, and there were minute areas of hemorrhage. The dilatation of the vessels is ascribed to paralysis of the vessels, and the hemorrhages to tearing of the vessels. Nippe believes that the histologic differences between the current mark and the lightning mark are due to the much greater intensity and the much shorter duration of the application of the lightning current. In the reported case of death due to lightning, except for the lightning marks and petechiae of the eyelids, sclera and pleura, the gross and microscopic observations were entirely negative. The immediate cause of instantaneous death from electric shock or lightning is asphyxia, but whether this is due primarily to cessation of the heart action or to cessation of respiration cannot be determined.

O. T. SCHULTZ.

RUPTURE OF THE HEART IN FALL FROM HEIGHT. O. BERNER, Norsk mag. f. lægevidensk. **93**:833, 1932.

A man, aged 28, fell from the fourth floor to the ground; death was almost immediate. A rupture about 9 cm. long, parallel to the axis of the heart, was found in the left ventricle of the heart; the edges were sharp and without extravasation of blood. The diaphragm was perforated. The rupture is explained by hydrodynamics. In this instance the possibility of a bone fragment as the cause of the rupture of the diaphragm and heart was excluded. The rupture of the diaphragm occurred where the heart in its upright position rests on the diaphragm; the patient fell on his chest, and the thorax, because of the fracture of the clavicles and of ribs on the left side, may be assumed to have been comparatively easily pushed in from above downward and toward the spinal column. It is therefore concluded that the heart caused the rupture of the diaphragm, and then directly afterward was itself ruptured, owing to the pressure. Other observations were a fracture of the base of the cranium and particularly of the frontal bone, and hemorrhages both in the lateral ventricles and in the fourth ventricle, and characteristic ecchymosis over the left nucleus caudatus.

Society Transactions

BUFFALO PATHOLOGICAL SOCIETY

Regular Meeting, Dec. 17, 1932

KORNEL TERPLAN, *President, in the Chair*

DIFFUSE SARCOMA OF THE DURA MATER WITH UNUSUAL RESTRICTION OVER A SINGLE HEMISPHERE. J. LANG.

An 11 year old white boy was admitted to the Buffalo City Hospital on March 11, 1932, with a history of a sudden attack of severe frontal headache, nausea and projectile vomiting, followed by delirium, rigidity of the neck and inability to use the fingers of the left hand. The knee jerks were hyperactive, and the Brudzinski, Babinski and Kernig signs were elicited bilaterally. The spinal fluid was clear and under a pressure of 40 mm. of mercury. The patient was discharged after eighteen days' observation. For two weeks he remained without symptoms. One month later he was seen complaining of headache. There was a reduction of vision in the left field, with beginning atrophy of the disk. Three months after the first admission he was readmitted because of atrophy, persistent headache, sleeplessness and vomiting. The fundi showed the effect of increased intracranial pressure. Daily spinal puncture gave relief. The fluid was always clear; the pressure ranged from 20 to 50 mm. of mercury. The condition became progressively worse, the patient dying four months after the first admission.

At autopsy the right parietal bone showed two well defined thinned transparent areas, each measuring 6 cm. across. A tumorous proliferation was noted on the inner surface of the dura, involving the entire right side and measuring from 4 to 8 mm. in thickness. Its surface was dull gray, irregular and nodular. This thickened area tapered gradually at the periphery. Medially it terminated from about 5 to 8 mm. from the falx cerebri; laterally and inferiorly, at the level of the floor of the anterior and middle cranial fossae. There were also two discrete white nodules measuring 4 mm. in diameter on the anterior portion, and 3 mm. on the posterior portion, of the adjacent side of the falx cerebri. On section the tumor was gray and homogeneous. The underlying cerebral convolutions were flattened and showed several white areas, which on section proved to be small tumor masses grouped around blood vessels. There was slight narrowing of the right lateral ventricle and dilatation of the left. Other postmortem observations were not remarkable.

Microscopically, the tumor was a primary alveolar sarcoma of the dura mater, showing a fine stroma in which were embedded masses of cells of alveolar structure. These cells were uniform in size and had large nuclei and a narrow rim of cytoplasm. The stroma was made up of fine interlacing strands of connective tissue, and was quite vascular. Sections from the white areas of the cerebrum revealed a thick layer of tumor spreading along the vessels, leaving the lumens and large areas of brain tissue between the vessels free. No nerve elements or glia were demonstrated by various special methods. The brain was apparently involved by direct contact.

DISCUSSION

K. TERPLAN: The extension of this tumor resembles somewhat a primary sarcoma arising in the leptomeninges, a malignant neurogenous tumor or glioma of the retina, which often show diffuse invasion of the entire subarachnoid space. The gross specimen in Dr. Lang's case indicates clearly the primary origin in the dura mater. The histologic picture is well in line with this conception. The small round cells resemble somewhat the endothelial cells in meningiomas. But

here the more diffuse sarcomatous structure seen in alveolar sarcoma is present rather than the typical picture of meningioma.

I recall a primary round cell sarcoma of the dura mater, which I examined post mortem in Dr. Ghon's Institute in Prague, in a white man. The tumor originated in the right medial fossa and only locally invaded the temporal lobe as well as the underlying bone.

ANOMALOUS DRAINAGE OF THE PULMONARY VEINS IN THE PORTAL SYSTEM, AND OTHER CONGENITAL MALFORMATIONS OF THE HEART COMBINED WITH SITUS TRANSVERSUS. K. TERPLAN and WINFIELD L. BUTSCH.

A white girl lived nine and a half hours after birth. She was intensely cyanotic. Oxygen and digitalis were administered but to no avail. The clinical diagnosis of congenital cardiac disease was made by Dr. F. C. Goldsborough. The anatomic diagnosis was: mirror image situs transversus, transposition of the great vessels, patent septum primum et secundum, persistent left superior vena cava, anomalous drainage of the azygous vein into the left superior vena cava, cor triloculare biatriatum, complete stenosis of the pulmonary artery, anomalous drainage of the pulmonary veins into the portal circulation, an anomalous celiac artery, mesenterium commune and an exceptionally hypoplastic lentil-sized spleen.

The complete absence of pulmonary veins entering the left atrium was the most unusual finding. No veins were seen at any place on the anterior aspect of the atria or ventricles, nor were any noted entering the venae cavae. On the posterior surfaces four veins were seen coming from the upper and lower lobes of both lungs, uniting to form a common trunk which was about 8 mm. in circumference and lay to the right of the vertebral column. There were three branches, one to the esophagus, a large one to the stomach and a third to the region of the duodenum. The lungs showed a marked degree of alveolar and interstitial emphysema. The surface of both lungs was glistening and covered with fine dewlike vesicles.

Only one similar case was found in the literature, that reported by C. H. Hu (*Am. J. Path.* **5**:389, 1929). In this case the pulmonary artery, although hypoplastic, was still patent. The anomalous drainage of the pulmonary veins in the portal system was essentially the same. In Hu's case the spleen was entirely absent.

A complete report of this case will be published later.

ANOMALOUS ORIGIN OF THE LEFT CORONARY ARTERY FROM THE PULMONARY ARTERY; MYOCARDIAL DEGENERATION AND FIBROSIS OF THE LEFT VENTRICLE, WITH A PARTIAL ANEURYSM AT THE APEX. S. SANES and F. E. KENNY.

An Italian girl, aged 3 months, was admitted to the Children's Hospital, Nov. 1, 1932, because of vomiting of three weeks' duration. Shortly after the onset of emesis, which occurred two or three times a day, cough appeared. Three days before the patient's admission to the hospital breathing became difficult and rapid. The child was born at full term and weighed 7 pounds (3,175 Gm.). No cyanosis was noted at or after birth. Examination showed: temperature, 97 F.; pulse rate, 140; respirations, from 40 to 50; retraction of the intercostal spaces bilaterally on inspiration; dulness throughout the whole left side of the chest with râles. The heart was markedly enlarged; no murmurs were heard; the sounds were distant. The liver was palpable. Within several hours after admission to the hospital, the child died. Necropsy revealed: an anomalous origin of the left coronary artery from the pulmonary artery; marked fibrosis and calcification of the left anterior papillary muscle; fibrosis of the myocardium of the left ventricle with a partial aneurysm of the anterior wall at the apex and septum; marked dilatation of the left ventricle with distinct hypertrophy of its wall, especially toward the base (weight of the heart, 95 Gm.); distinct fibrosis of the endocardium of the left ventricle and atrium; parietal thrombi of the left ventricle; moderate hydroperi-

cardium; slight passive congestion of the liver and kidneys; compression atelectasis of both lungs with lobular pneumonia in the left upper lobe; a low position of the diaphragm; a concave depression in the superior surface of the left lobe of the liver, and a bulging deformity of the left thoracic wall. The foramen ovale and ductus arteriosus were closed. Except for the abnormality mentioned, the coronary vessels were normal. The line of ossification was regular. The histopathologic changes were restricted to the left ventricle. They consisted of endocardial fibrosis, various types of myocardial degeneration, necrosis, reactive cellular inflammation, fibrosis and calcification.

A thorough search of the literature disclosed only five similar cases. The pathologic observations were traced to the anomalous origin of the left coronary artery from the pulmonary artery with resultant anoxemia of the myocardium of the left ventricle. The left ventricle was supplied by venous blood. Whether carbon dioxide in excess had a specific detrimental effect on the heart was difficult to judge. As an embryologic explanation, Abrikosoff suggested that if the anlage of the left coronary artery took origin in the thickening of the aortic bulb at the left, slightly anteriorly to the usual site, the orifice would be incorporated in the pulmonary artery above its left valve after complete formation of the aortic septum, dividing the bulb into aortic and pulmonary trunks.

(A complete report of this paper will appear in the *American Journal of Diseases of Children.*)

CEREBRAL ARTERIES IN RELATION TO ARTERIOSCLEROSIS. C. R. TUTHILL.

A complete report of this paper will be published in the ARCHIVES.

LYMPHOSARCOMA OF THE RETICULUM CELL TYPE. MARGARET WARWICK.

Three cases of lymphosarcoma of the reticulum cell type were presented. All three growths had several characteristics in common. Each was composed of large cells with pale vesicular nuclei and a moderate number of mitotic figures. Also present were numerous large multinucleated cells with similar nuclei but practically no lymphocytes. Each of the tumors arose in a group of lymph nodes, and showed metastases to organs other than lymph nodes. In each case but one group of nodes was involved, and death was caused by progressive cachexia.

The outstanding gross features of the tumors were given briefly:

CASE 1.—In a man, aged 66, the primary tumor arose in the mediastinal lymph nodes with invasion of the right lung. This mass was firm, white and large, practically filling the right pleural cavity, compressing the superior vena cava and infiltrating the right auricle with complete penetration of the wall and the formation of tumor nodules on the inner surface. Metastases could not be demonstrated except in the left kidney, which retained its shape but which was entirely infiltrated with the tumor cells. Some of the glomeruli and tubules were still visible in the masses of tumor cells.

CASE 2.—In a man, aged 50, the primary tumor arose in the retroperitoneal lymph nodes on the right side, forming a soft, bulky, lobulated white mass which appeared to be invading the adjoining structures. The metastases were all in the bones and were demonstrated in the spine, sternum, ribs and femur. Although bulky soft tumors surrounded the bones at the sites of the metastatic tumors, roentgenograms showed no replacement of the bone. Instead, as demonstrated by microscopic sections, the tumor cells filled the haversian canals and infiltrated the bone without destroying its structure.

CASE 3.—In a boy, aged 13, the primary tumor arose in the mediastinal lymph nodes, giving an appearance similar to that in case 1. It was a very firm, white mass which invaded the left lung and filled the entire pleural cavity. The only metastatic tumor was a small nodule, about 2 cm. in diameter, in the lower lobe of the right lung.

DISCUSSION

K. TERPLAN: I think that a careful histologic analysis usually enables the pathologist to differentiate between special types of lymphosarcoma and other conditions producing grossly almost identical pictures, such as Hodgkin's disease and so-called Hodgkin's sarcoma. Recently, in Germany, Roulet applied the term "retothelial sarcoma" to lymph node tumors of the reticulum cell type. It may be said, however, that from Roulet's description it is not altogether clear whether all the cases presented in his first paper were those of reticulum cell sarcoma. Complete postmortem examination sometimes changes the diagnosis made originally from observations at biopsy. In about twenty cases examined in the past two years in our hospital it was possible to distinguish histologically between lymphosarcoma and Hodgkin's disease.

Regular Meeting, Feb. 11, 1933

KORNEL TERPLAN, *President, in the Chair*

SICKLE CELL ANEMIA WITH AUTOPSY. NORMAN HEILBRUN.

A Negress, aged 50, was taken ill with chills, fever and a productive cough ten days' prior to admission to the hospital. Her past history revealed that she had pains in the joints as a child, and ten years before admission had two attacks of a condition called rheumatic fever. There was no history of any familial dyscrasias of the blood.

On admission, the temperature, pulse rate and respirations were elevated. The patient was of short stature and quite obese. The chest showed signs of consolidation at the base of the right lung with many moist and sibilant râles. The heart was enlarged to the left, and the blood pressure was 206 systolic and 120 diastolic. There were no ulcerative lesions found on the extremities.

There were 3,100,000 erythrocytes, with 42 per cent hemoglobin (Newcomber), and 32,000 leukocytes, with a marked predominance of the polymorphonuclears. The fixed smear showed marked variation in size and shape, with much achromia and 80 per cent nucleated erythrocytes. An occasional sickle cell was seen. The reticulocytes were 20 per cent. Wet films showed complete sickling in from four to six hours. The van den Bergh reaction and icteric index were normal; the urobilinogen was not increased. The fragility of the erythrocytes ranged from 0.44 to 0.2. A normal control ranged from 0.44 to 0.32. The Kahn test was negative. Pneumococci found in the sputum were type IV. The other laboratory findings were normal. The clinical diagnosis was bronchopneumonia and sickle cell anemia.

Shortly after admission the symptoms cleared, and the leukocytes decreased to 14,000, the polymorphonuclears still predominating. On the eleventh day after admission, signs of pneumonia again appeared. The patient was placed in an oxygen tent. After five days in the tent, sickling was not evident in wet films until thirty-six hours' after the films were made. Subsequent attempts to produce this effect in a similar manner on the son who has the sickle cell trait failed. The patient died sixteen days after admission.

Autopsy was performed by Dr. Kornel Terplan. There were: bronchopneumonia of the right lower lobe with recent pleuritis; a chronic splenic tumor with thickening of the capsule, the weight being 350 Gm.; hyperplasia of the bone marrow; hypertrophy of the left ventricle with slight fibrosis, and slight hemosiderosis of the liver. The anatomic diagnosis was bronchopneumonia and sickle cell anemia.

Microscopic examination showed several interesting changes. In the spleen, the malpighian bodies were almost completely lacking. The pulp was engorged with great masses of sickle-shaped erythrocytes, while the sinusoids were relatively

empty. Most of the arterioles had moderate hyaline thickening. Here and there was slight fibrosis of the reticulum fibers of the pulp. With an iron stain there were many pigmented endothelial cells, especially around the trabeculae and in the subcapsular spaces. Smears of the bone marrow showed a marked predominance of myelocytic elements with many normoblasts and an occasional megaloblast.

The liver showed slight atrophy of the cords with sinuses filled with sickle-shaped erythrocytes and slight periportal round cell infiltration. The Kupffer cells contained many pigment granules, and an occasional cell showed phagocytosis of erythrocytes. Scattered throughout the parenchyma were small proliferations of endothelial cells, some of which showed pigmentation and phagocytosis. With the iron stain most of the Kupffer cells showed distinct pigmentation.

The reticulum cells of the lymph nodes showed distinct proliferation with occasional phagocytosis of erythrocytes and some deposits of hemosiderin.

In the kidneys there were mild vascular changes. In many of the fibrotic areas was a marked exudation of polymorphonuclears—an acute interstitial nephritis. This was most likely due to the terminal infection.

This case presented the interesting changes of distinct focal endothelial cell hyperplasia in the liver and acute interstitial nephritis in addition to the typical pathologic changes of sickle cell anemia.

CIRRHOSIS OF LIVER FOLLOWING MILD TOXIC DYSTROPHY (SO-CALLED CATARRHAL JAUNDICE) SIX YEARS PREVIOUSLY. RAYMOND S. ROSEDALE.

Autopsy on a woman, aged 23, showed toxic cirrhosis of the liver with huge nodules of regenerative hepatic cells. Inquiry of the parents revealed that when 17 years of age the deceased suffered upper abdominal distress followed by intense jaundice, which persisted for about six weeks. The urine was said to have been coffee-colored. The patient was not hospitalized. The entire period of illness embraced about three months. Since that time her health had been good. She had married within the last year. Three days before her death she became dizzy and vomited a slight amount of blood. Following a large hematemesis, she died unexpectedly.

At autopsy the peritoneum was found to be distinctly wet with a slight amount of free fluid in the pelvis. The liver weighed 725 Gm.; the surface showed hazelnut-sized nodules with intervening, depressed, firm areas. Some areas showed lobular structure of the liver with congestion of the central zone. The cut surface exhibited irregular bile-stained nodules of the parenchyma of the liver surrounded by fibrous stroma. The consistency on palpation was more nearly like that of a normal liver, being somewhat flaccid with wrinkling of the surface, in sharp contrast to the more unyielding character in Laënnec's cirrhosis.

The spleen weighed 200 Gm. and was firm. The veins of the lower part of the esophagus were tortuous, enlarged and thin-walled. A minute erosion was found that admitted a probe.

Microscopically, the liver revealed the changes of a typical chronic dystrophy or toxic cirrhosis (Mallory) with huge nodules of regenerative hepatic cells, collapse of the hepatic stroma and numerous bile ducts.

DYSTROPHY OF THE LIVER IN A TABETIC PATIENT AFTER THERAPY WITH ARSPHENAMINE. S. SANES.

A white man, aged 39, complained of urinary frequency and incontinence, and pain in both legs for one year. He also suffered with epigastric pain and emesis. He said that he had never had a penile lesion. The pupils were fixed. Deep reflexes could not be elicited in either leg. The Romberg sign was positive. The Kahn test of the blood and the spinal fluid gave positive results. The clinical diagnosis was tabes dorsalis and peptic ulcer. The patient received 0.4 Gm. of arsphenamine on July 27, and Aug. 3, 1932. A severe reaction with fleeting jaundice

followed the second dose. On August 10 and 17, 0.3 Gm. of silver arsphenamine was given in split doses. Transient jaundice again appeared. The administration of silver arsphenamine, 0.3 Gm., was continued for three doses. Fifteen doses of bismocymol, 1.5 cc., were administered from September 21 to December 7. Acute jaundice developed on December 7; the liver was palpable three fingerbreadths below the costal margin. The laboratory findings included urobilinogen, positive in a dilution of 1:10; dextrose, 98 mg. per hundred cubic centimeters; urea nitrogen, 15 mg. per hundred cubic centimeters; immediate van den Bergh reaction, positive, 25 units; icteric index, 100 plus. Duodenal drainage was negative for pathogenic bacteria. A twenty-four hour sample of urine contained from 16 to 20 mg. of arsenic. Approximately four weeks after the onset of jaundice the skin was clear; the liver was not palpable. The urine showed no bile. The van den Bergh reaction was less than 0.6 units. The patient died on Jan. 28, 1933, from bleeding gastric ulcer and ascending pyelonephritis.

The gallbladder and bile ducts were free. The liver weighed 1,000 Gm. Its margins were sharp. In the right lobe was found a dime-sized, circular, grayish-red area showing no lobular structures. The remainder of the liver presented normal markings.

Histologically, the lobules showed uniformly distinct degeneration of the hepatic cells in the paracentral zone with necrosis. The cells contained greenish-brown pigment which proved to be bile and partly hemosiderin. The central veins appeared dilated. The paracentral reticulum was collapsed following the disappearance of the hepatic cells. In other parts of the lobules regressive changes were also noted. The Kupffer cells were distinctly swollen. The small focal area noted grossly in the right lobe showed nodular regeneration of the hepatic cells, proliferating bile ducts and fibroreticular scarring.

The similarity between the changes in the liver in this case and those seen in a case of jaundice following immediately after the injection of arsphenamine was suggested. Attention was called to the discrepancy between the results of various tests for hepatic function and the actual presence of hepatic damage, as shown in this case.

INGUINAL LYMPHOGRANULOMA. K. TERPLAN.

The histologic sections in two typical cases of inguinal lymphogranuloma were presented, and the differential diagnosis was discussed. Both cases were seen in Buffalo in the fall of 1931. The nodes were excised surgically. In the first case the gross appearance of resected inguinal nodes suggested the correct diagnosis. Smears taken from abscesses revealed no micro-organisms. The second case was seen clinically with bilateral enlargement of the inguinal nodes and acute inflammation of the skin overlying them.

It is believed that the diagnosis of inguinal lymphogranuloma can be made with certainty by histologic analysis. While some areas showed structures similar to epithelioid tubercles, the abscess formations with marked necrobiotic changes in degenerating epithelioid cells and the absence of true caseation spoke in favor of a diagnosis of inguinal lymphogranuloma rather than of tuberculosis. In addition, the diffuse infiltration of the lymphoid structures between abscesses was more multiform than is usually seen in tuberculosis. Often plasma cells, and especially mononuclear giant cells resembling pictures in Hodgkin's disease, were seen about the abscesses. Examination of different parts of lymph nodes must be made, for some sections may show only nodular structures with epithelioid cells in which necrobiotic disintegration and abscess formation have not yet taken place. And here the condition may easily be mistaken for tuberculosis.

Material obtained from the second case was injected into five guinea-pigs. All reacted after a few days with distinct swelling in the area in the abdominal wall into which the injection was made, but without remarkable involvement of the lymph nodes. These experimentally produced infiltrates ranged from the size of a hazelnut to that of a plum. After from ten to fourteen days, they retro-

gressed gradually and finally disappeared. Second transmissions were made from the acute infiltrates without other effect than a slight local reaction. The guinea-pigs were observed from four weeks to one year. Autopsy did not reveal a spread to the lymph nodes. There was only a localized reaction in the abdominal wall, the histologic picture of which appeared as a simple foreign body reaction. Two rabbits were also given injections, but showed no reactions. These observations do not confirm the work of K. Meyer and H. E. Anders, who felt that it is easy to produce experimentally inguinal lymphogranuloma in guinea-pigs and that the spread of the infection closely resembles that of tuberculosis.

The Frei test was made in the first case one year after removal of the nodes, and a distinctly positive reaction was obtained. The second patient could not be obtained for the test.

CEREBRAL ANEURYSMS IN RELATION TO ARTERIOSCLEROSIS. C. R. TUTHILL.

This paper will be published in full in a later issue of the ARCHIVES.

PRIMARY SARCOMA OF THE GREAT OMENTUM. S. SANES and F. E. KENNY.

The clinical, operative and postmortem observations in three cases of primary sarcoma of the great omentum were presented. In 1930, Grieg referred to fifty-seven authentic cases of this disease, reported in the literature.

CASE 1.—A white boy, aged 16 years, complained of pain in the upper part of the abdomen and loss of weight for several months. In the left side of the hypochondrium, palpation revealed a lemon-sized mass which was firm, irregular, movable and tender. Laparotomy disclosed a huge quantity of bloody fluid in the abdominal cavity. A soft, irregular, circumscribed tumor, 14 by 11 by 12 cm., in the great omentum was removed. This growth was bluish red and distinctly cystic. The histologic diagnosis was reticular cell sarcoma with many multipolar cells showing threadlike cytoplasmic radiations and with numerous mononuclear and polynuclear giant cells. The patient died shortly after operation from intra-abdominal fetid abscess in connection with a sinus in the transverse colon, streptococcic thrombophlebitis of the superior vena cava, multiple emboli in branches of the pulmonary artery, infarctions of the lungs and soft splenic tumor. Microscopically, a remnant of the tumor was found in the mesentery.

CASE 2.—A white man, aged 48, consulted a physician because of severe abdominal pain, nausea and emesis of five days' duration. The abdomen was distended and tympanitic; no mass was felt. The temperature was 99 F. Laparotomy revealed about 800 cc. of foul-smelling, purulent material in the peritoneal cavity. The great omentum was adherent to the abdominal wall and viscera. About 50 Gm. of tissue was removed. This specimen consisted of many small nodules of growth which was firm but friable. The histologic diagnosis was large spindle cell sarcoma. The patient died twelve days' postoperatively. Autopsy showed remnants of a primary spindle cell sarcoma of the great omentum, sarcomatous adhesions to the ileum, solitary metastasis to the liver, fetid intra-abdominal abscess in connection with a sinus in the ileum, fibrinous peritinitis and bronchopneumonia of both lungs.

CASE 3.—A white woman, aged 66, complained of progressive enlargement of the abdomen for six months. The abdomen was markedly distended; the superficial veins were dilated, and fluid was present. No mass was felt. Death occurred suddenly four days after admission to the hospital. Autopsy revealed diffuse endothelioma apparently originating in the great omentum, with dissemination to the mesentery, serosa of the gallbladder, parietes, uterus, diaphragm and left pleura. Hemorrhagic ascites and hemothorax in the left side were present. Death occurred from pulmonary embolism.

The first case is of surgical importance because it suggests that early excision of circumscribed tumors might afford a favorable prognosis.

NEW YORK PATHOLOGICAL SOCIETY

Anniversary Meeting, Jan. 26, 1933

PAUL KLEMPERER, *President, in the Chair*

OBSERVATIONS ON THE RETICULOCYTES OF PIGEONS. ELIZABETH N. DAVIDSON.

Studies of the reticulocytes were made on pigeons' blood. The method consisted in diluting the blood with a vital stain (azure B), allowing it to stand for twenty minutes, preparing a dry cover slip of smears from the dilution and counterstaining with tetrachrome. It was found that less than 1 per cent of the red cells of pigeons are nonreticulated, and that the reticulation occurs in an infinite number of degrees varying from a barely perceptible amount to an almost complete filling of the cell. There occurs only one type of reticulated cell which can be definitely distinguished from the others by the fact that its reticulum appears as a halo about the nucleus. This cell maintains a fairly constant incidence, averaging 8.7 per cent, with variations from 7 to 10 per cent. An attempt is being made to study the possible change in the percentage of occurrence of this type of cell after feeding and after the injection of liver extract.

CONGENITAL ABSENCE OF THE VERMIFORM APPENDIX. SOUTHGATE J. GREEN and WILLIAM J. ROSS.

Green and Ross report a case in which the absence of the appendix was well established by laparotomy, performed because of a clinical diagnosis of acute appendicitis, and by detailed histologic studies following postmortem examination. On the basis of their thorough study of this case, a review of the literature, and some personal observations, they point out: (*a*) the difficulty of proving true agenesis of the vermiform appendix at operation, (*b*) the possible unfortunate results of too diligent operative search for this organ, and (*c*) the desirability of distinguishing between hypoplasia and agenesis. The number of reported cases of agenesis of the appendix is estimated at 26 (21 additional cases reported as instances of this condition are unacceptable either because of lack of proof or because they were instances of hypoplasia). The pathologic changes responsible for the symptoms and signs of acute appendicitis in the case studied were not ascertained.

DISCUSSION

ALFRED PLAUT: What was the cause of the original acute illness which led to the operation?

SOUTHGATE J. GREEN: We examined the gastro-intestinal tract, the genito-urinary tract, the pancreas and the gallbladder, endeavoring to determine the factor responsible for the pain, but were unable to do so. We also asked Dr. Spain, of the clinic for the treatment of patients with allergy, of the New York Post-Graduate Medical School and Hospital, whether the pain might have been due to food poisoning. The patient said that he had had an acute attack of pain, a year previously after eating canned corn and that he had not eaten this food again until just before the onset of the present illness, which seemed to him to be similar to the first attack of pain except that it was more severe. Dr. Spain said that the only evidence of food poisoning that would be demonstrable in the sections would be an increase in the eosinophils, and this we were unable to detect. We were therefore unable to ascertain the cause of the illness which led to the operation.

GAUCHER'S DISEASE WITH UNUSUAL TERMINAL FEATURES. LOUISE H. MEEKER and SAMUEL J. BOCHNER.

In a case of Gaucher's disease in which autopsy was performed there was a history of splenomegaly of long duration.

A Jew, 65 years of age, had been examined thirty-five years before admission to the hospital and was told that he had an enlarged spleen. At that time, the blood picture, including the platelet count, was normal. After about thirteen years with no improvement, roentgen therapy was given for one year. Burns developed in the skin over the area treated, and treatment was discontinued. The ulcerated areas were a source of discomfort until death. This largely overshadowed the distress caused by the "pressing weight" of the enlarged spleen.

The patient came to the New York Post-Graduate Medical School and Hospital on Oct. 25, 1932, complaining of severe attacks of biliary colic which had begun a month previously. Cholecystotomy with removal of gallstones was done. The surgeon noted many gray and red nodular masses in the massively enlarged spleen and liver and suggested a diagnosis of metastatic carcinoma. Biopsy specimens were taken from a nodule of the liver and from the lesions of the skin. The pathologist reported chronic nonmalignant ulcer of the skin and reticulo-endothelial lipomatosis of the liver (Gaucher). Two days later the patient died. The blood, even during the last illness, was fairly normal. Among the cases of Gaucher's disease that have been reported we have found but one other case in which roentgen therapy was used on the basis of an empiric diagnosis of splenomegaly. Irradiation was without effect in that case also.

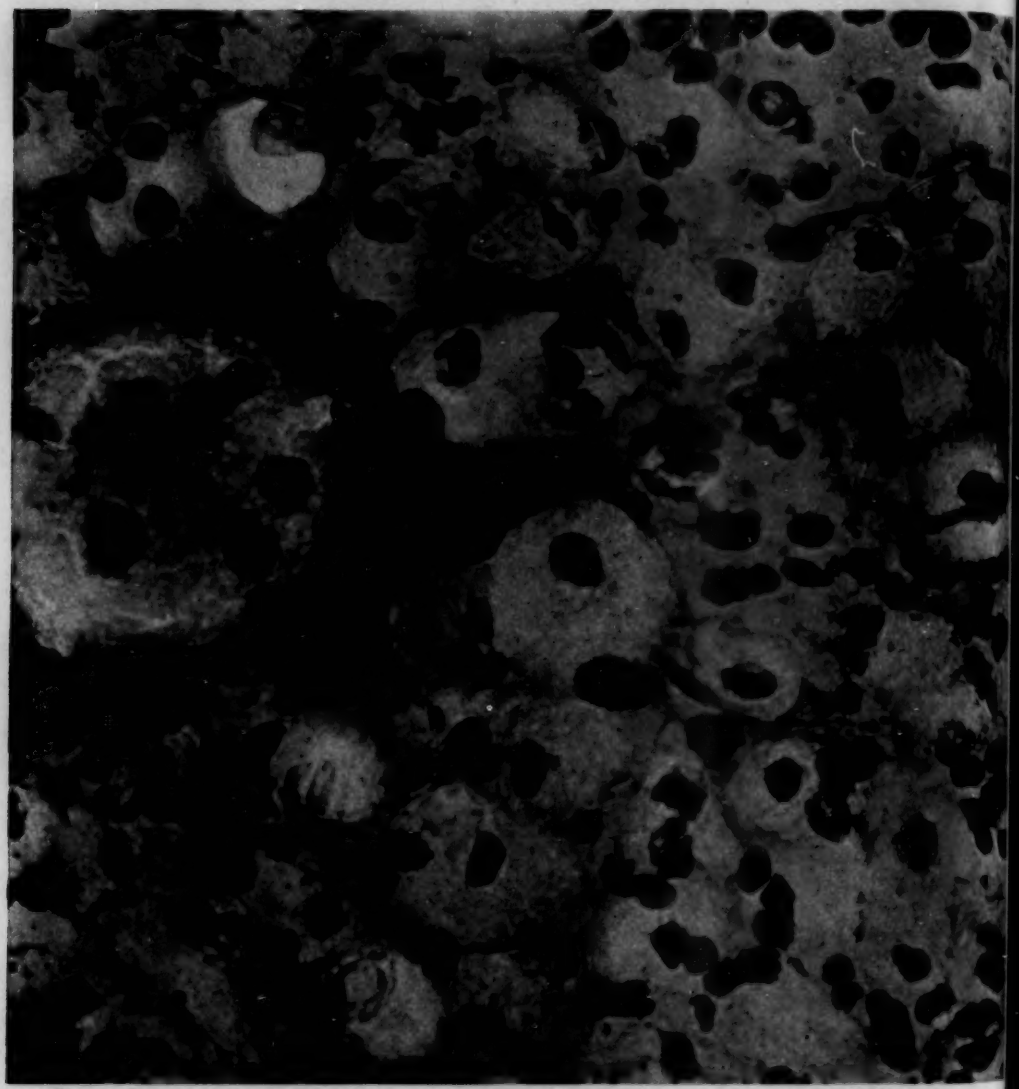
Necropsy, limited to the region about the abdominal incision, was performed forty minutes post mortem. The body was well developed. General icterus was marked. Pingueculas were not present. The abdominal skin in the splenic region showed ulceration and cicatrization. The superficial lymph nodes were not palpable. There was no gross evidence of a pathologic process in the bones. The spleen weighed 4,635 Gm. The surface was bossed by rather irregularly rounded red to yellow nodules. The cut surface was rather dry and the scrapings were cell-poor. The characteristic architecture of the spleen was not recognizable. The liver weighed 3,570 Gm. The surface was bossed by small and large rounded, yellowish masses, in part isolated and in part confluent. The cut surface presented numerous, large and small yellow masses, the largest of which showed central hemorrhages. The substance of the liver was firm and presented the picture of biliary cirrhosis. The mesenteric lymph nodes were soft and freely movable. The largest of these measured 10 mm. in diameter. The cut surface was yellow.

The structure of the spleen, liver and lymph nodes showed extensive replacement of the normal elements by the large pale cells of Gaucher's disease. Many of these cells were multinucleated and measured from 20 to 75 microns in diameter. Large cell masses were occasionally noted; one, apparently a syncytial mass, measured 350 microns in diameter. The masses formed a prominent part of the picture in all sections of the spleen, appearing as group and islands and in many areas presenting an alveolar arrangement. The pale cells were similar in all respects to those described by Gaucher, Bovaird, Mandelbaum, Schlagenhaufer and others, and variously named epithelioid, endothelial, lipoid, histiocytic and Gaucher's cells. With Bielschowsky's silver impregnation method the reticular fibrils were seen to surround, and in places appeared continuous with, the substance of the Gaucher cells. Further studies are needed. Smears of the fresh splenic pulp were stained with the tetrachrome stain for blood (fig.). They showed large pale cells, almost equaling the leukocytes in number and varying from 40 to 100 microns in diameter. Many were multinucleated, some having thirty nuclei. Some of the larger cells showed phagocytosis. Sections of the skin of the abdomen showed ulceration and scarring but no malignant process.

The use of special methods for identifying the lipoid content of the large clear cells typical of Gaucher's disease yielded nothing more than other observers have reported. These studies indicate that the pale cells of the Gaucher type are filled chiefly by the cerebroside group of lipoids. Stains for iron showed a scant quantity in occasional Gaucher's cells, and in these areas the reticulum similarly showed some iron.

Summary.—This case was proved to be one of Gaucher's disease by the history and the gross and microscopic changes. The picture was obscured by ulceration

of the skin (caused by roentgen therapy) of twenty-two years' standing and by the lack of symptoms other than the cutaneous lesions, as well as by the gross appearance of the spleen and liver at the time of operation. Death was due to intercurrent factors, cholelithiasis and the shock of a major operation. The salient



Smear of fresh splenic pulp stained by the tetrachrome stain for blood. The large pale cells are the Gaucher cells. One on the left side is multinucleated.

features of the history are the patient's race (Jewish), his age (65 years), the splenomegaly of thirty-five years' duration and the absence of changes in the blood. In the microscopic studies special stains and examination by polarized light cor-

roborated the findings of other observers regarding the lipoid content of the Gaucher cells, their iron content, meager in this case, and their relation to the reticulo-endothelial system. The mesenteric lymph nodes were of special importance.

DISCUSSION

PAUL KLEMPERER: In the last six years my associates and I have seen eight patients with Gaucher's disease; four of them died, and four were operated on, so we were able to study the spleen. Reports of five cases have been published by Drs. Oppenheimer, Rosenthal and Welt; three have not been published. One of the latter was particularly interesting, because the condition was accidently found at autopsy in a man of 72 who had died of carcinoma of the pancreas. His spleen weighed only 500 Gm. The bone marrow showed nests of Gaucher's cells. This case shows that the disease may develop even in the late years of life.

I think that the case presented is interesting because of the correlation of the condition with roentgen treatment; dermatologists agree that roentgen treatment is of little value in Gaucher's disease, and this case proves it.

A. A. EISENBERG: Two weeks ago my associates and I observed a case of Gaucher's disease in a Jewess, 55 years of age; the spleen weighed 7.2 Kg. (about 15½ pounds).

THERAPEUTIC USE OF BACTERIOPHAGE AGAINST COLON BACILLI. WARD J. MACNEAL, FRANCES C. FRISBEE and MARTHA APPLEBAUM.

The development of a bacteriophage against the colon bacillus presents the same problem whether the organism infects the urinary tract, the blood stream or the intestinal tract. The bacteriophage of the colon bacillus has a high specificity. This necessitates the use of a large number of races, each highly potent and multivalent, in the preparation of individual lytic agents for therapy. The individual lytic agents are prepared by adapting a stock race of bacteriophage to the infecting organism. Various principles which must be borne in mind in using this form of therapy are: the necessity for careful control of the hydrogen ion concentration of the infected region; the necessity for close contact between the infecting agent and the lytic agent, and the inadvisability of using antiseptics at the same time that bacteriophage is used.

Four cases of colon bacillus septicemia are reported, with recovery in 3 instances. Colon bacillus bacteriophage in asparagine was injected intravenously. The use of the bacteriophage in colitis was followed by improvement but was not markedly successful. More than 250 patients with acute or chronic pyelitis have been treated with bacteriophage by subcutaneous injection, instillation through the bladder and intravenous injection of the asparagine preparation, in varying combinations. The p_H of the urine was carefully controlled. Clinical success was evident in more than half the cases, and in some instances the results were dramatic.

A bacteriophage which is so active as to cause complete destruction of the organism becomes an effective weapon against colon bacillus infection in any part of the body.

NOTE.—This work was supported by a grant from the Josiah Macy, Jr., Foundation.

STREPTOCOCCUS BACTERIOPHAGE AND STREPTOCOCCUS CULTURE FILTRATES IN THE TREATMENT OF ENDOCARDITIS LENTA. WARD J. MACNEAL, MARGARET E. STRAUB and MARTHA JANE SPENCE.

During a period of eighteen months, seven patients suffering from endocarditis lenta were treated with autogenous filtrates of broth cultures of streptococci to which bacteriophage had been added. Six died, and one is still under treatment. The patients received the culture filtrate and also blood serum from donors who

had been treated with the same filtrate. Apparently the course of the disease was somewhat altered, but there is no reason to claim any success.

NOTE.—This work was supported in part by a grant from the Josiah Macy Jr., Foundation.

THE HEART IN A CASE OF ENDOCARDITIS LENTA AFTER TREATMENT WITH BACTERIOPHAGE. REUBEN MACBRAYER and SAMUEL J. BOCHNER.

A white man, aged 29, who had had attacks of rheumatism twelve years previously, was treated intensively for subacute bacterial endocarditis by subcutaneous and intravenous injections of a culture filtrate of Streptococcus viridans which had been inoculated with streptococcus bacteriophage and by weekly transfusions of blood from donors immunized by injections of the same material. After three months' treatment he died. Detailed histologic study of the heart revealed strikingly the following changes, at least some of which are unusual in subacute bacterial endocarditis: (1) an inflammatory process, mainly productive, involving the endocardium; (2) a pancarditis which was traced from the endocardium to and through the epicardium, producing pericarditis; (3) severe myocardial inflammation and degeneration, especially of the left side of the heart; (4) few evidences of the rheumatic lesions, and (5) numerous polymorphonuclear leukocytes and monocytes containing phagocytosed streptococci. We believe that the productive inflammation and phagocytosis were favorably influenced by the therapy.

The paper just presented by Dr. MacNeal and his associates set forth the technic of this therapy and the clinical results in seven patients.

DISCUSSION OF PAPERS ON BACTERIOPHAGE

ALFRED PLAUT: Is there a possible relation between any unusual changes in the heart and the treatment in the case reported by Dr. MacBrayer and Dr. Bochner? Or does the opinion prevail that the same lesions might have been present without treatment with bacteriophage?

PAUL KLEMPERER: The lesions in this case were distinctly productive. However, as the picture in subacute bacterial endocarditis is extremely protean, one might, in studying a number of cases, find identical changes; hence I should not lay too much stress on the lesions in the heart as evidence of the influence of treatment. In fact, subacute bacterial endocarditis is characterized by a much more productive type of lesion than is acute bacterial endocarditis, in which an exudative necrotizing lesion predominates.

Phagocytosis is found in untreated patients as well. The giant cells which one finds frequently in lesions of subacute bacterial endocarditis often contain bacteria.

I feel that one cannot gain much encouragement from the histologic picture in this case; but of course it is one case only, and the clinical features in the other cases are possibly more significant.

GEORGE BAEHR: The work reported has been painstaking, and it has taken courage to reopen the subject of the therapy of subacute bacterial endocarditis. The pathologists with whom I am associated who have been studying the disease for several decades have been discouraged by the monotony of the bad results. Few of us have seen any patients get well. A few cases in which recovery occurred have been reported in the literature, and Dr. Libman has seen patients recover spontaneously, become reinfected and again recover. I have seen one or two patients become bacteria-free spontaneously, and later die from reinfection. We have followed a few hundred cases clinically, and have been fortunate in seeing 170 autopsies; from the latter we have learned little concerning why some patients become bacteria-free. Of the 170 patients that came to autopsy, 59 died in the bacteria-free stage of the disease. The remarkable thing is that every one of the 59 patients became bacteria-free spontaneously, shortly after the onset of the disease. In the rest of the 170 patients, bacteria were constantly in the blood

stream during the many months from the time of infection until death. The patients in whom an infection of the heart valves with anhemolytic streptococci develops are of two types: Either the immunologic mechanism is intact and they become bacteria-free immediately after the onset of the disease, or they never kill all the bacteria on the heart valves. Those who become bacteria-free shortly after the onset of the disease have the same pathologic lesions, the same infarction and the same embolic glomerular lesions as the others. But the embolic glomerular lesions in the kidney are much less numerous, because the infectious stage of the disease has been shorter. The majority of persons in whom the valves of the heart become infected with this organism of low virulence seem to possess no resistance to infection and never kill all the bacteria. The number of bacteria in the circulating blood fluctuates from day to day, depending on the number swept off mechanically from the vegetations, but the total number in the blood stream is kept fairly well in check, possibly by phagocytosis and other methods of removal. As Dr. Klemperer has emphasized, not infrequently there are numbers of phagocytes in the vegetations, and there may also be a great deal of organization in some of the vegetations, particularly when the infection has been present for a long time before death. In spite of the discouraging results which have just been described, and in spite of the fact that the blood stream in the cases reported has not become bacteria-free, it is by some such persistent and courageous effort that the means of sterilization of the blood and of the valves of the heart may eventually be discovered. Unfortunately even this may not be a complete answer to the problem, for all of the 59 patients whom we have seen in the bacteria-free stage of the disease have died as a result of the progressive anemia, of asthenia or of the embolic phenomena of subacute bacterial endocarditis. One third of the patients who became bacteria-free (19 of 59) died in a state of uremia following glomerulonephritis, a complication which rarely occurs in the patients who do not kill all the bacteria.

WARD J. MACNEAL: We undertook to do this work on subacute bacterial endocarditis largely because the work was forced on us. Patients have been referred from other hospitals and sent by physicians who were under the impression that because we had attained some success in the treatment of bacteremias due to staphylococci and the colon bacillus, we might obtain equal success in this field. I am much disheartened by the results in these cases of endocarditis, and I should long ago have refused to undertake the handling of any more cases of this kind had it not been for the enthusiasm of those associated with me. I am grateful to them for their enthusiasm, and I am on my feet to express my satisfaction in being associated with persons who are still willing to tilt at windmills.

Regular Monthly Meeting, Feb. 23, 1933

PAUL KLEMPERER, *President, in the Chair*

PATENT VENTRICULAR SEPTUM WITH MURAL ENDOCARDITIS DUE TO STAPHYLOCOCCUS ALBUS. LAWRENCE H. COTTER.

A patient came to Gouverneur Hospital with a typical picture of sepsis; he had a septic temperature, and showed numerous petechiae, enlargement of the spleen and heart murmurs and a marked thrill in systole and diastole. The heart showed signs of considerable hypertrophy. The rate was rapid. There were a high white cell count and a high polymorphonuclear count. Repeated blood cultures showed Staphylococcus albus.

Autopsy showed marked hypertrophy of the right and left ventricles and a round hole in the interventricular septum about 2 cm. in diameter, just below the valve attachments. On the wall of the right ventricle opposite this opening the endocardium was thickened, and there was a cauliflower-like vegetation attached

to the thickened endocardium. This vegetation was very soft, friable and roughly spherical, measuring about 3 cm. in diameter. There were infarcts and small abscesses in the lungs and numerous infarcts in the spleen and kidneys. There was no involvement of the endocardium around the hole in the septum. Dr. de la Chapelle has two specimens with patent interventricular septums and Streptococcus viridans at the margins of the openings, but I have seen none like this.

PRIMARY LIVER CELL CARCINOMA. VERA D. DOLGOPOL.

G. M., a white man, aged 83, entered the hospital because of edema of the legs. He died nine days later of a condition that was diagnosed as chronic myocarditis and cirrhosis of the liver.

At autopsy an ascites of 2,000 cc. was found. The liver was diminished in size, but was not cirrhotic. The right lobe, in its upper part, contained a massive necrotic tumor 11 cm. in diameter, with macroscopic extensions; the microscopic structure was that of a primary liver cell carcinoma. Macroscopic thrombi of tumor tissue were present in the portal vein, in the larger hepatic veins and in the small branches of the right pulmonary artery. Tumor nodules measuring up to 1 cm. in diameter were present in the right lung. No abdominal lymph nodes were involved.

Cirrhosis is absent in only 15 per cent of cases of primary carcinoma of the liver.

DISCUSSION

LAWRENCE H. COTTER: Can someone tell me roughly what proportion of these tumors do not show metastases?

VERA DOLGOPOL: Tumor metastases in the lungs occur in about 20 per cent of cases, and at that the lungs are organs in which there is rather frequent microscopic involvement. In general, liver cell carcinoma is not an easily metastasizing tumor.

PAUL KLEMPERER: Two years ago I had an unusual opportunity to observe a primary carcinoma of the liver in a patient who had been given thorotrast. It was most interesting that the Kupffer cells in the cirrhotic part of the liver contained thorotrast, while the endothelial cells within the primary carcinoma did not, a fact which proved the contention that has been held for years, that the endothelial cells within a primary carcinoma of the liver are not of the Kupffer cell type.

A RARE CASE OF ULCERATIVE JEJUNITIS (SYPHILITIC?). S. H. POLAYES and J. R. PEARSON (by invitation).

A white youth, 17 years of age, was admitted to the Jewish Hospital of Brooklyn on Aug. 12, 1932. He had been treated in the outpatient department for a month previously for the following symptoms which had occurred during the past year: abdominal pain, loss of weight, night sweats, a rise in temperature in the evening and, more recently, diarrhea and fecal vomiting. Physical examination led to a diagnosis of tuberculous peritonitis with adhesions, causing intestinal obstruction. The latter was confirmed by roentgen studies. The various laboratory tests (studies and chemical analyses of the blood, Wassermann and Kahn tests and examinations of the stools and urine for parasites, typhoid, dysentery and tubercle bacilli) were negative. The patient was advised to have an operation, but refused. He died on December 12.

Postmortem examination showed the following changes: ulcerative jejunitis with multiple strictures, ascites, fibrosis of the lung, spleen and pancreas and fat replacement of the liver.

The following conditions were excluded by postmortem examination of the tissues and by various clinicopathologic tests: tuberculosis, dysentery, typhoid, parasitic infections (ameba and actinomycosis), Hodgkin's disease and neoplasms (lymphoblastoma, sarcoma and carcinoma). Of the other two possible conditions, nonspecific enteritis and syphilis, the latter was considered to be the more probable

diagnosis because of the striking similarity between the intestinal lesions in this case and those in the previously described authentic cases of syphilis of the intestines. The lesions were described as follows:

The duodenum and jejunum were markedly distended with gas to a point about 15 cm. above the ileojejunal junction. At this point there was an irregular band of constriction in the wall of the jejunum, 2 cm. in width, producing a stricture which almost completely obliterated the lumen of the organ. A similar band of constriction was present distally at the ileojejunal junction. The mucous membrane lining the jejunum was the seat of numerous superficial and deep ulcers, transverse as well as longitudinal to the axis of the intestine. The ulcerative process was most marked in the distal 15 cm. of the jejunum between the two constrictions. Here the chronic ulcerative process had produced bridging of the mucosa and nodular thickenings in the wall, the latter simulating tumors. On section, however, the thickenings were found to be due to chronic inflammatory changes in the wall opposite the ulcers.

Microscopic sections through the jejunal ulcers showed large portions of mucous lining destroyed and replaced by exudate which consisted of fibrin and polymorphonuclear as well as mononuclear and plasma cells. The structure beneath this layer was made up entirely of granulation tissue. This tissue was infiltrated with round cells and plasma cells. There was an accompanying marked fibroblastic reaction. The blood vessels were exceedingly numerous in this area and were thick-walled, presenting marked endothelial proliferation of their intimal linings. The veins as well as the arteries participated in this process. At the junction of the submucosa and the muscularis there were occasional multinucleated giant cells surrounded by round cells. There were no epithelioid cells.

The muscularis mucosae was extremely hypertrophied, and in the ulcerative areas was distorted by the infiltrative and granulomatous changes. Beneath this layer the infiltrate assumed a focal character, forming discrete collections of round cells with a tendency to perivascular infiltration. In some of these lesions there was an excessive amount of scar tissue.

The muscularis and serosa showed a less extensively destructive process, but here also the chronic inflammatory nature of the disease was marked, especially in the serosa, where the tendency to perivascular round cell infiltration was most evident.

Levaditi, Jahnel and Starry-Warthin stains of the scrapings of the ulcers showed the presence of structures resembling Spirochaeta pallida. Acid-fast stains were negative for tubercle bacilli; bacteriologic studies were negative for dysentery and typhoid bacilli. Stains for parasites were negative.

This case is presented as an extremely interesting problem with the purpose of receiving any helpful suggestion so as to arrive at a definite diagnosis.

DISCUSSION

SYLVAN E. MOOLTEN: Would Dr. Polayes be willing to make any estimate of the probable duration of the illness?

PAUL KLEMPERER: Were there changes in any other organ indicative of syphilis?

DAVID PERLA: I listened to the case very carefully. I do not see any evidence of its being one of syphilis. The history is that of a youth of 17. There is no history of syphilis, and the morphology is certainly not in favor of syphilis. I cannot make out from your description, from the histologic preparations or from the lantern slides, and I had occasion to examine the sections, that there is any definite evidence of syphilis. The finding of a few things which may look like spirochetes on the surface smear of the intestinal tract would hardly be convincing. I think that it would be much wiser to diagnose this case as one of chronic ulcerative jejunitis of unknown etiology. There is no crime in not knowing the etiology of a disease; by that I mean that you would be much wiser in limiting yourself to facts and not trying to make a definite diagnosis when no definite diagnosis

can be made. I do not think that any one would be able to make a diagnosis in a case of this type from the postmortem material.

PAUL KLEMPERER: Dr. Polayes is at a disadvantage in not being able to present his evidence in lantern slides as well as by the microscope. We are also at a disadvantage in that we cannot judge from the few photomicrographs presented, but there is a Committee on Microscopy to which I think these sections should be submitted for an opinion.

S. H. POLAYES: With regard to the age of the lesion, from the clinical history, the lesion was active for nearly two years. Of course, if it is syphilitic, it is possible that the condition was hereditary.

In reply to Dr. Klemperer's question concerning the findings in other organs of the body, I believe that the interstitial fibrosis which was found in the pancreas and which we know is not so common a finding in ordinary cases of enteritis might be considered of syphilitic origin. The same may be said of the pulmonary fibrosis. Although neither of these changes can be considered definitely syphilitic, it must be pointed out that in only a few of the so-called authentic cases of syphilis of the intestines were definite evidences of syphilis found in other organs.

With regard to Dr. Perla's comment, I should like to repeat that a definite diagnosis of syphilis was not made in this case, nor was any importance attached to the findings of spirochetes in the smears from the surface of the ulcers. The case is presented for discussion and for any suggestion one may offer as an aid in determining the etiology. Although a diagnosis of syphilis cannot be made with certainty in this case, it must be pointed out that if this is not a case of syphilis, then the etiology of the previously reported cases which were based on the same histopathologic changes as were found in the present case will also have to be doubted. If the previously reported cases can be considered authentic, one cannot exclude the diagnosis of syphilis in this case, in view of the striking similarity between the lesions in this case and those in the so-called authentic cases of syphilis of the intestines.

A LYMPHOCYTE HEMOGRAM. CARL REICH.

Based on the work of Wiseman, who showed that basophilia of the cytoplasm is a constant and reliable criterion of the age of lymphocytes, I undertook a series of studies to see whether a classification of lymphocytes according to the degree of basophilia would be of clinical value. The type of cases selected was widely diversified and represented all types from the very sick to the ambulatory patients with minor complaints. The patients were studied at biweekly intervals during their stay in the hospital. Suitable controls were employed.

Technic.—White and differential counts were made for each observation. The Wright-Giemsa stain was used. The lymphocytes were divided into three classes, Y, M and O, according to the degree of basophilia of their cytoplasm. The Y forms had a deep blue cytoplasm; the M forms, moderately blue, and the O forms, faintly blue or colorless. The percentage of each form was calculated, the procedure being similar to that used in determining the Schilling index. There is a constant lymphocytic formula for normal persons. For adults this can be expressed as Y forms 5 per cent, M forms 50 per cent and O forms 45 per cent. Variations occur in this formula under different conditions, and one can therefore speak of a shift to the left or to the right of the lymphocytic index, depending on whether the number of younger forms is greater or lesser than normal. A comparison with the Schilling index in each case shows that the two do not run parallel. The lymphocytic index is not as stable as the Schilling index and will shift to the left just as easily in a mild as in an acute infection. Even though the lymphocytic formula cannot be used to gage the severity of an infection, its shift to the left in these conditions nevertheless indicates that lymphocytes take an active part in combating bacterial invasion, as is seen by the increase in Y and M forms and the decrease in O forms in practically all cases of infection. The lability of the lymphocytic hemogram makes it valuable in the detection of minor infections which

do not disturb the more stable Schilling index. Interesting and confirmatory evidence for using basophilia as a criterion of the age of lymphocytes is seen in the study of the lymphatic leukemias. In these cases there is a marked increase in the proportion of Y and M forms, indicating the well known hyperactivity of the lymphatic system in this disease. In the myeloid leukemias there are also an increase in lymphocytic activity and a shift of the index to the left. It is of interest to note also that according to the lymphocytic index the period of convalescence is probably much longer than is usually expected.

DISCUSSION

MAURICE MORRISON: I looked very carefully at the first picture showing the different types of cells. There was one cell which showed a marked basophilia but no nucleoli. One large cell had slight basophilia and contained nucleoli. It was my impression that the first cell was an ordinary lymphocyte, while the other one was a lymphoblast. I should not use basophilia alone as an index of youth. I should use it only in conjunction with the other morphologic characteristics of the cell, especially the presence or absence of nucleoli.

ALFRED PLAUT: Has there been any opportunity to examine the lymphocytic index in typhoid fever, or the so-called infectious mononucleosis? Also in case there is a shift in the lymphocytic index in infection, does it prove that they take an active part in combating the invader? It seems to me it shows only that they react.

ARTHUR SCHIFRIN: Was the lymphocytic index studied in any cases of agranulocytic angina?

MAURICE RICHTER: Does Dr. Reich consider all the Y forms, particularly in the normal blood smear, as lymphoblasts? The ones he has in his illustration are apparently of that type. Plasma cells and so-called Türck irritation forms have basophilic cytoplasm, and their presence might cause a shift to the left. I should also like to ask whether there is a shift in noninfectious conditions.

CARL REICH: So far as the question of lymphoblasts and nucleoli is concerned, Naegeli and all the hematologists insist that the chromatin and nucleoli are important in the differentiation of cells. Most of the lymphoblasts show a fairly deep blue cytoplasm, and the Y form—the ordinary deeply stained lymphocytes—are not supposed to be the same age; they are merely younger than those which are very pale.

I think that Dr. Plaut is perfectly right. The shift probably indicates an activity of the lymphocyte, but just what that is, I do not know.

I have not had an opportunity to study agranulocytic angina, nor a chance to study the lymphocytic index in enough cases of typhoid fever. I have had only one case of infectious mononucleosis which was of the monocytoid type. As I did not have an opportunity to study more of these cases, I did not think it fair to say anything about them.

In reply to Dr. Richter's question, I can say that in normal persons and in those with a cold, sinus trouble or arthritis, there was a shift. The point concerning the plasma cells and the Türck irritation forms is important; I do not recall seeing a great many of them. I think that they can be classified with the Y forms.

MAURICE RICHTER: Is there a shift to the left during convalescence?

CARL REICH: I think that there probably is a shift during convalescence.

INTRANUCLEAR INCLUSIONS IN TUMORS OF THE BRAIN. ABNER WOLF.

In studying a series of tumors of the brain during the past year, unusual intranuclear structures were observed in some of the cells in a certain percentage of the neoplasms. The intranuclear bodies resemble in many respects those found in many of the virus diseases. They are acidophilic in staining reaction, have sharp margins,

often have a halo around them and are single or multiple. They vary considerably in size, ranging from 3.5 microns in diameter to 9.7 by 12.7 microns.

In sections stained with hemotoxylin and eosin, the intranuclear structures are seen as eosinophilic rounded masses with distinct contours and often with a thin dark blue rim. The smaller bodies are deeply colored, whereas the larger ones are much paler. They are either homogeneous or finely granular and often show more concentrated central or eccentric areas. In the majority of instances a clear zone or halo is found about them. The nuclear chromatin tends to clump and collect along the nuclear membranes. At times the clear space is not so well defined, the chromatin being irregularly distributed and in contact with the inclusion along a considerable portion of its border. Often the chromatin is very dense and less distinctly particulate and fills almost all of the nucleus about the inclusion. Occasionally only a few chromatin particles are seen between a large inclusion and the adjacent membrane, or the scant chromatin radiates in strands from the inclusion. The nucleoli are basophilic, although at times they too are eosinophilic and have a thin blue margin. At times they are pressed toward the margin of the nucleus, and occasionally they are not found.

The inclusions occur most often in uninucleated or multinucleated giant cells, but they may occur within cells of the whole range of the given tumor. The nuclei containing them may be regular in outline, or they may have wrinkled or serrated margins.

The inclusions are found exclusively within tumor cells and not in the ganglion or glia cells of the adjacent or invaded nervous tissue. Four or five may be found in one low power field, sometimes many within one nucleus, or often only a single inclusion is found in an entire section.

One hundred and sixty-five tumors of the central nervous system were examined: 100 gliomas, 60 mesodermal tumors and 5 tumors of the pituitary body. Twenty-five per cent of the gliomas showed inclusions of the type described. The greatest number was found among the neoplasms classified as glioblastoma multiforme. Thirty-three of these tumors were examined, and 16, or almost half, showed intranuclear inclusions. Four of 17 medulloblastomas, 1 of 28 fibrillary astrocytomas, 2 ependymomas and 1 neuroblastoma showed such intranuclear structures. Sixty mesodermal tumors were examined, and of these 15 showed intranuclear bodies. They were most frequently encountered in the meningeal fibroblastomas, of which 32 were examined, and 9 showed inclusions. Of 12 perineurial fibroblastomas, 5 showed inclusion bodies. None of the adenomas of the pituitary body showed inclusions.

Dorothy Russell in a recent publication reported the finding of inclusions in all essential respects like those reported here in a third of a series of 192 gliomas examined. She stated that "if they indicate a virus infection, it is probable that the virus is the cause of the tumor."

If it is conceded that my inclusions and those described by Russell are the effect of a virus and not merely a degeneration phenomenon in spite of Cowdry's warning "that the presence of intranuclear inclusions in unknown conditions should not be taken at face value as indicating the action of some filtrable virus," their etiologic significance would not yet be established. Rivers and Pearce showed that viruses (virus III and vaccine virus) multiplied rapidly in a transplantable tumor in a rabbit and were carried along with the tumor through an indefinite number of transplantations. Findlay and Ludford reviewed a group of cases in which intranuclear inclusions were found and in which no active virus disease was present. One must, therefore, seriously consider whether the virus present in the tumors of the brain studied is not merely an incidental inhabitant. I believe that it is impossible to say from my finding of intranuclear inclusions in such tumors of the brain that either the gliomas or the mesodermal tumors of the central nervous system are caused by a virus or viruses. Only the production of similar tumors by the filtrate from such tumor material with the reproduction of intranuclear inclusions would be conclusive.

DISCUSSION

DAVID PERLA: I think that intranuclear inclusions are fascinating things. I have seen them repeatedly in many different varieties of conditions. One sees them in all forms of malignant neoplasms. They are frequently seen in squamous cell carcinoma of the skin: eosinophilic inclusions of the nucleus. Many good pathologists have stumbled badly on these intranuclear inclusions and have drawn erroneous conclusions and deductions. The fact that in virus diseases one sees peculiar inclusion bodies, most of which one knows nothing about and does not understand, does not mean that the presence of similar eosinophilic bodies limited to the nuclei in neoplasms bears any relation to virus disease. I think that if one examines a number of conditions other than tumors of the central nervous system, one finds that they bear no definite relationship to tumors of the central nervous system as such. The closing sentence of Dr. Wolf's paper was extremely apropos, and one should be more than cautious in suggesting a relationship of virus diseases to tumors from the appearance of nuclear bodies. Just what they mean is difficult to say, because one does find them in actively growing cells in which there is no evidence of any degeneration, but that they have any significance so far as indicating the presence of a virus condition, either complicating or etiologic, there is no evidence.

S. H. POLAYES: In a case of psittacosis which my associates and I had the opportunity to study, we found inclusion bodies in some of the cells, but they were not necessarily limited to the nucleus. They were in the cytoplasm of the cells as well. While listening to Dr. Wolf's paper, this question arose: Why, if caused by a virus, does the inclusion body always attack only the nucleus? One would expect to find some cells in which the peculiar inclusion body was in the cytoplasm as well as in the nucleus.

ABNER WOLF: I am glad to hear that Dr. Perla agrees with me in my conclusions.

In regard to Dr. Polayes' question, there are virus diseases in which the inclusion bodies are typically only in the nuclei and do not occur in the cytoplasm. The inclusions seen in the neutrophic virus diseases are almost all of that type, and it may well be that if the condition presented is a virus, it is one of that type.

LIPOSARCOMA, INTRACANALICULAR FIBROMA, PERICANALICULAR FIBROMA AND CYSTIC CHANGES OF THE BREAST. MAX LEDERER and (by invitation) SAUL LIVINGSTON.

This case is reported because of its rarity and the multiplicity of lesions in one breast.

A Jewish woman, aged 44, was admitted to the hospital on Sept. 22, 1932. She stated that three weeks prior to admission she noticed a lump in the right breast, which had not increased in size, been painful or throbbed. The skin over it was never red. She does not remember ever having hurt her breast, and no discharge from the nipple was noticed.

Physical examination revealed a rather apprehensive woman in good health. General physical examination revealed nothing abnormal. The nipples were normal in appearance; the breasts were symmetrical. A tumor mass about 5 cm. in diameter occupied the lower outer quadrant of the right breast. The tumor was hard in consistency, moved freely in the breast, felt rather circumscribed and was not attached to the deeper parts. The axillary lymph nodes were not enlarged.

The operative procedure consisted in a thoracomammary incision, exposing the posterior aspect of the breast. A large encapsulated growth was enucleated. The tumor was lobulated, yellowish white and soft. A frozen section showed it to be a liposarcoma. The breast was removed, and the axilla was cleared of all fat and lymph glands. The postoperative course was uneventful except for a rise in temperature of from 1 to 2 degrees on the first and second days. The wound healed well, and the patient was discharged six days after operation.

Four months after operation the patient's general condition was excellent; the scar over the right side of the chest was freely movable, and there was no local recurrence. Roentgen examination of the chest showed no metastasis.

Macroscopic examination of the breast showed it to consist of several portions: (*A*) There was a tumor which appeared lobulated, was oval, measured 5 by 3 by 4 cm. and was ocher-colored. The consistency was rubbery; the surface was smooth. On section it was seen to be made up of numerous lobules of yellow tissue with a homogeneous appearance. (*B*) Other portions contained similar yellow tissue, which was softer and more distinctly lobulated. Scattered throughout were smaller nodules of the same appearance. In one portion of the specimen was a papillomatous mass arising by a narrow pedicle from a smooth lining membrane. This mass was translucent and presented a papillomatous appearance. (*C*) The breast proper contained solid nodules which somewhat resembled the tissue first described. *D*) There was fat at the distal points. (*E*) The lymph nodes were enlarged.

Microscopic examination of the main tumor showed it to consist mostly of cells which varied greatly in size, and in the hematoxylin-eosin stained preparation it appeared mostly as clear spaces surrounded by a delicate cell membrane. Occasionally white trabeculae divided the spaces into two or more compartments; some contained a very delicate fibrillar network. The nuclei occupied various positions in the cell, some being centrally, while others were eccentrically, located. The nuclei varied greatly in size and shape; some were intensely hyperchromatic, and an occasional nucleus showed a mitotic figure. In some instances there was more than one nucleus, while in others the cells appeared to be polymorphic. Scattered throughout were collections of cells with a pink-staining granular protoplasm, some of which contained a few small clear spaces. An occasional giant cell with a huge nucleus was encountered. There was no regular arrangement of the deposits in the cells, and with van Gieson and Mallory stains the tumor was found to contain very little fibrous tissue. Very few blood vessels were found, and those present consisted mostly of spaces lined by a single layer of endothelium and surrounded by abundant fibrous tissue. A few small round cells were scattered here and there.

Sections prepared from frozen material and stained with sudan III showed most of the cells to be filled with fat droplets. These globules were relatively small and appeared as distinct globules in the cells. Careful study led one to the conclusion that the cells which made up the tumor consisted of fat cells in various stages of development, from the stage in which there was no differentiation and the protoplasm appeared granular to the stage of full maturity in which the cells contained numerous droplets of fat.

Sections taken from the polypoid mass showed it to consist of a very loose myxoma-like stroma arranged in a polypoid formation, the external surface being covered by a single layer of epithelium.

Sections of other tumefactions in the breast showed a marked fibrous tissue about ductlike structures in which the fibrous tissue was rather dense and the ducts were lined by cuboidal epithelium.

Sections from other portions of the breast showed what appeared to be a marked increase in the density of the stroma, with a mild round cell infiltration. The ducts in these areas were markedly dilated and were lined with one or two layers of cuboidal epithelium. The lymph glands showed only an inflammatory hyperplasia and no malignant process.

It appears that the breast was the seat of four separate and distinct lesions, namely, pericanalicular fibro-adenoma, intracanalicular fibro-adenoma with marked edema, cystic degeneration and liposarcoma.

DISCUSSION

WILLIAM ANTOPOL: I should like to know whether this case may be considered one of lipoma rather than liposarcoma, and also whether the lipomatous changes in the sections may not be similar to those seen in primary xanthoma (Haagensen,

C. D.: *Am. J. Cancer* **16**:1066, 1932) or in xanthoma secondary to fibro-adenoma, chronic cystic mastitis and other chronic inflammations. The foam cells on the screen resemble those found in these conditions.

PAUL KLEMPERER: The question of embryonal fat cells is difficult. I am inclined to regard as embryonal fat cells polygonal cells which have not one large fat droplet but in which the cytoplasm is honeycombed by the presence of many small fat droplets. This type of fat cell is occasionally found in fat tumors and suggests that one is dealing with an embryonal fat tumor which is called, therefore, a liposarcoma. Two facts have caused me to reconsider the point of view that I have held for a considerable time: I made a study of the embryonal development of fat tissue based on the work of Wassermann in 1926. This author showed that embryonal fat tissue develops from definite mesenchymal foci, which are called primordial fat organs (Toldt). These primordial fat organs consist of reticulated mesenchymal cells which have not yet differentiated to the type of connective tissue cells which are recognized in the mesenchyme in adult life. In fact, the development of the fat tissue begins at about the same time the lymphatic tissue develops from the embryonal mesenchyme. The mesenchymal foci which later develop into lymphatic tissue have exactly the same arrangement and structure as the embryonal primordial fat organs of the human embryo in the fourth month of life. In these stages the fat cell is really an undifferentiated embryonal cell and does not have the appearance of the polygonal cell which has been called the embryonal fat cell. If one studies the fat in lower mammals, one will find that there are two forms of fat present, the white or yellow fat and the brown fat. The brown fat is particularly found in hibernating animals, in which it forms a large glandular mass. It is peculiar that this fat in hibernating animals is composed of polygonal cells. In human beings one finds the same type of polygonal cell, particularly around the thymus region. It is furthermore possible that the ordinary fat cell in a condition of starvation takes on the appearance of the polygonal cell with multiple fat droplets.

In regard to fatty tumors which are composed exclusively of this type of polygonal cells, I have had one case in which I could follow up the patient for many years. The patient, whom I saw nine years ago at the Post-Graduate Hospital, had a tumor which I regarded, because of its histology, as a possible embryonal fat tumor; I suggested that the surgeon watch the patient carefully. I inquired about the patient seven years later when I was studying embryonal fat tumors, and I was told that the patient, who had only a simple excision of the tumor, was in perfect health. This experience, combined with other experiences, has caused me to reconsider the point of view that one should regard these tumors as sarcomas.

In the case reported there were two cells which showed amitotic figures. These figures are also encountered in the type of polygonal fat cell tumor which I should hesitate to regard as a liposarcoma. The question arises, Does a liposarcoma exist at all? Generally malignant tumors which contain fat are found in combination with other embryonal tissue, particularly, as Dr. Lederer has said, with myxomatous tissue. The existence of a liposarcoma, a tumor consisting only of fat cells, is in my opinion questionable. I have seen one tumor which caused me to study the whole question. It was a malignant, recurrent type of tumor which was observed for nine years, and which consisted entirely of embryonal fat tissue in a very early developmental phase. This tumor did not conform with the polygonal fat cell tumor described by Dr. Lederer and Dr. Livingston. There is, furthermore, a theoretical question regarding the designation of a tumor as a sarcoma if it does not consist of connective tissue.

I should like to ask Dr. Lederer why in a case like this a radical operation was performed? Do you recommend the removal of the lymph nodes in the axilla in all cases of sarcoma of the breast?

MAX LEDERER: This case gave us a good deal of cause for study, and the points brought out were fairly well considered. It is probable that we may be accused of a considerable amount of temerity in presenting this case as one of liposarcoma, but we should not have done it without the diagnosis of Dr. Ewing,

who thought that the tumor was a liposarcoma. The lantern slides do not give all the information that is available in this case. As Dr. Klemperer remarked in connection with the previous case, we are at a disadvantage in trying to prove our case by lantern slides, but certain parts of the tumor illustrated by one of the slides consist of compact cells which look sarcomatous and which are undifferentiated. It is not an inflammatory lesion; it is definitely neoplastic. As we studied the sections, we found what we thought might be gradations in the development of the cells from the undifferentiated cell to an adult fat cell, or clear spaces as the fat cells are ordinarily recognized in sections stained with hematoxylin and eosin. Some of the spaces are enormous. The frozen section, which was carefully studied, showed the appearance Dr. Klemperer mentioned, namely, a scattering of fat droplets in the cell bodies. In some instances the cells were packed with these bodies; in others there were only a few, and one could still make out an undifferentiated eosinophilic protoplasm. The tumor bears no resemblance to a xanthoma. That diagnosis was excluded promptly. Furthermore, the amount of inflammation in the breast was very slight; even in the small areas where there occurred cystic disease, there was very little round cell infiltration.

I think that the intracanalicular fibro-adenoma and its cystic appearances were due more to edema than to myxomatous tissue.

We are perhaps adopting a more or less independent attitude in calling the tumor a liposarcoma, but I think that we have just as much reason for calling it that as have those who argue that there is no such thing, because if there can be a fibrosarcoma and a myosarcoma, why cannot there be a liposarcoma? Microscopic study shows that the tumor is malignant; it is not histologically a benign one.

Concerning the radical operation, we have a radical surgeon, Dr. William Linder, at the Jewish Hospital who does not take any chances. He says that rather than expose a patient to a study, which would answer a question of purely academic interest, he would sacrifice the breast. Perhaps he is right. The lymph nodes do not show a malignant process, but he argues that if one waits until they do show definite signs of malignancy, it is too late.

The conclusion concerning this case, especially after fortification by Dr. Ewing's opinion, is that we are dealing with a liposarcoma. It is a most peculiar tumor. There was another nodule in the breast at a distance from the original one which was shelled out. We are thankful for the criticisms or suggestions which may throw light on the specimen. If this case shows further developments, they will be reported.

ALFRED PLAUT: I have seen pseudoxanthomas in my gynecological work at the Woman's Hospital, and I do no think that any pseudoxanthoma I ever saw was like the one under discussion, no matter what kind of inflammation caused it. Guided by accidental findings, I have made for a long time a study of fat giant cells, and I do not think that outside of malignant tumors I have ever seen any fat giant cells like these. A few weeks a go I saw a large liposarcoma of the mesentery which did not contain any other tissues; the resemblance of this tumor to the one demonstrated by Dr. Lederer and Dr. Livingston is very striking. I should have diagnosed this tumor as a liposarcoma without hesitation. If the patient remains well for many years, I should still call the tumor a liposarcoma, and state merely that liposarcomas are clinically benign.

Book Reviews

A Study of Nephritis and Allied Lesions. By John Gray. Medical Research Council, Special Report Series, no. 178. Price, 2s. 6d., net. Pp. 141. London: His Majesty's Stationery Office, 1933.

The book is an excellent example of a recent type of pathologic studies in which a serious attempt is made to correlate gross and microscopic structural changes with the clinical manifestations of disease. It is based on an examination of the kidneys in more than 500 cases and is an analysis of the histologic and clinical findings in all those in which nephritis or an allied type of lesion was evident. This is the second comprehensive study of this subject published by the Medical Research Council, the first being that of Dorothy Russell in 1929 (reviewed in ARCH. PATH. **10**:344, 1930).

The present monograph is divided into twelve chapters. The introductory chapter states the objects of the investigation, presents a critical discussion of the general principles of classification of nephritis, sets forth the methods employed and describes briefly but adequately the normal and general pathologic histology of the kidney. The succeeding chapters deal with the various types into which the author classifies the disease: acute nephritis, acute focal nephritis, acute nephrosis, subacute and early chronic nephritis, nephrotic nephritis, chronic nephritis, kidney of essential hypertension (arteriolosclerotic kidney) and arteriosclerotic kidney. The last group is considered of little significance as, of itself, the lesion produces no renal clinical phenomena and is characterized by arteriosclerotic focal atrophy. A small group of selected cases is presented with an adequate degree of completeness to illustrate the characteristics of each group.

The main object of this investigation was an attempt to devise a classification of nephritis which would be applicable both clinically and pathologically. The author recognizes the difficulties in framing such a classification. In the first place, two kidneys which are both grossly and microscopically so similar that they must be placed in the same pathologic category may have come from patients who showed fairly marked clinical differences (e. g., in degree of edema). In such cases the clinical data were analyzed with a view to determining whether there existed any underlying unity in spite of the presence of variable factors. In those cases which had some clinical features in common but which showed histologic differences search was made for other clinical features which might serve to distinguish between them. For purposes of classification, sets of clinical features were determined which characterize the different pathologic groups, and agreement between clinical and pathologic groupings was sought partly by attaching special importance to certain clinical features as against others. For example, in distinguishing chronic nephritis from conditions which resemble it in certain respects, such as essential hypertension and nephrotic nephritis, the ability of the kidney to produce a concentrated urine was considered of special importance.

The second difficulty in classification is that of delimiting the various groups from one another, for many of the groupings in any classification of nephritis must represent simply successive phases of the same condition, and inevitably many borderline cases must occur. To overcome this difficulty, descriptions of groups from either the clinical or the pathologic aspect have been composed of a range of possible appearances rather than of a single definite set of appearances. Advantage was taken of all natural clear lines of cleavage, such as are furnished by the first appearance of new features, or the disappearance of earlier ones. This plan was generally found suitable both from the clinical and from the pathologic point of view.

Whether or not the classification of nephritis presented in this monograph gains universal acceptance, it is a contribution to the subject that is worthy of consideration both by pathologists and by clinicians. Clearness in presentation compensates for the absence of illustrations.

Books Received

LYMPHATICS, LYMPH AND TISSUE FLUID. Cecil K. Drinker, B.S., M.D., Professor of Physiology, Harvard School of Public Health, and Madeleine E. Field, A.B., Ph.D., Instructor in Physiology, Harvard School of Public Health. Price, $3. Pp. 254. Baltimore: Williams & Wilkins Company, 1933.

URINE AND URINALYSIS. Louis Gershenfeld, Ph.M., B.Sc., P.D., Professor of Bacteriology and Hygiene and Director of the Bacteriological and Clinical Chemistry Laboratories, Philadelphia College of Pharmacy and Science. Pp. 272, with 36 engravings. Price, limp binding, $2.75, net. Philadelphia: Lea & Febiger, 1933.

DISEASES OF TRADESMEN. Bernardino Ramazzini (1633-1714). Together with biographical notes translated from the French of Francois Claude Mayer (1928) of Budapest and paragraphs from the preface of Dr. James (1746) of London, and of Dr. James (1922) of New York. The abstracts from the 1746 English Translation of the Ramazzini work emphasize his comments on dermatological disturbances of workmen. Compiled by Herman Goodman, B.S., M.D., New York City. With which is bound Silk Handler's Disease of the Skin, being a study of the clinical aspects, and a recital of the search for the cause including notes on the culture of the silkworm, the handling of the silk from the cocoon to its preparation in the throwing mill for weaving. Herman Goodman, B.S., M.D., New York City. Price, $1.50. Pp. 95, with 5 figures. New York City: Medical Lay Press, 1933.

CERVICO-VAGINITIS OF GONOCOCCAL ORIGIN IN CHILDREN. Report of a Project of the Bellevue-Yorkville Health Demonstration of New York City. Walter M. Brunet, M.D., Dora M. Tolle, M.D., Sara Alicia Scudder and Anne Ruth Medcalf. Foreword by Emily D. Barringer, M.D., Robert L. Dickinson, M.D., and William H. Park, M.D., Supplement No. 1 of Hospital Social Service Magazine. Price, paper, $2. Pp. 97, with illustrations. New York, 1933.

ARTERIOSCLEROSIS: A SURVEY OF THE PROBLEM. A Publication of The Josiah Macy, Jr., Foundation. Edited by Edmund V. Cowdry, Washington University, St. Louis. Price, $5. Pp. 617, with 88 figures. New York: The Macmillan Company, 1933.

EPIDEMIOLOGICAL STUDY OF SCARLET FEVER IN ENGLAND AND WALES SINCE 1900. Hilda M. Woods. Medical Research Council, Special Report Series No. 180. Price, 1s. 3d., net. Pp. 60. London: His Majesty's Stationery Office, 1933.

EXAMENS DE LABORATOIRE DU MÉDECIN PRATICIEN. Guy Laroche, Professor agrégé à la Faculté de Médecine; médecin des hopitaux de Paris. Troisième édition. Price, 50 fr. Pp. 492, with 151 figures. Paris: Masson et Cie, 1933.

A TEXT-BOOK OF NEUROPATHOLOGY. Arthur Weil, M.D., Associate Professor of Neuropathology, Northwestern University Medical School, Chicago. Price, cloth, $5, net. Pp. 335, with 260 engravings. Philadelphia: Lea & Febiger, 1933.

DIE HISTOPATHOLOGIE DER UTERUSMUCOSA. Ein Leitfaden für Gynäkologen und Pathologen bei der histologischen Diagnostik. Dr. H. T. Deelman, Ord. Prof. der Allgemeinen Pathologie und pathologischen Anatomie der Reichsuniversität Gröningen. Price, paper, 22 marks; bound, 24 marks. Pp. 247, with 248 illustrations. Leipzig: Georg Thieme, 1933.